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Editorial

Responsabilidade Social, Ensino, Hospitais e Sociedades Científicas
Social Responsibility, Teaching, Hospitals and Scientific Societies

Paula Freitas [a, b,*]

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O que é a responsabilidade social?

Originalmente, a responsabilidade social desenvolveu-se nas empresas a partir do movimento empresarial iniciado nos Estados Unidos na década de 1950, em resposta às pressões exercidas por movimentos sociais que acusavam o setor empresarial de se manter alheio aos problemas sociais de natureza variada – a pobreza, as desigualdades associadas à raça, ao género, à idade, etc., as condições de emprego e trabalho nocivas à saúde física e psicológica, a degradação das condições ambientais,- e exigiam que se tomassem diligências no sentido de compensar a sociedade pelos malefícios resultantes da atividade produtiva. Passou-se a exigir e a incentivar que as empresas adotassem práticas de responsabilidade social, para lá das estritas obrigações legais, enquanto ferramenta de orientação ética e prática. De um modo geral, a responsabilidade social trouxe para dentro do modelo de gestão organizacional, as preocupações relacionadas com os direitos humanos e do trabalho, a sustentabilidade, definida num sentido progressivamente mais amplo- económico, social e ambiental – e globalizado, e a participação democrática nos processos de decisão organizacional.

Para qualquer organização, a responsabilidade social é, atualmente, um fator determinante para o desenvolvimento e bem-estar de todas as partes interessadas e um dever e uma obrigação para com a sociedade em geral, na gestão dos impactos das suas ações. Ser uma organização socialmente responsável é também um fator de excelência e de reconhecimento de toda a comunidade e uma oportunidade de melhoria contínua.

E a responsabilidade social nas instituições de ensino superior?

Diversas instituições do ensino superior portuguesas (IES), elaboraram o primeiro Livro Verde sobre "Responsabilidade social e instituições de ensino superior", que foi lançado e apresentado em 2018. A estrutura do livro é baseada na tripla missão de uma IES - ensino, investigação e transferência de conhecimento - e na conceptualização da responsabilidade social universitária, na qual a universidade tem impactos na governança, formação, cognição e participação social.

O Livro Verde está organizado em quatro capítulos: 1) *campus* socialmente responsável; 2) formação pessoal e profissional dos estudantes e relacionamento com *alumni*; 3) gestão socialmente responsável da produção e difusão do conhecimento e; 4) participação social na comunidade.

No contexto do ensino superior existem duas áreas distintas, mas que se sobrepõem: o domínio da responsabilidade social e o domínio da sustentabilidade. Mais, considera-se que a responsabilidade social deve ser sustentável, podendo ser chamada de responsabilidade social sustentável.

As universidades devem ter um papel cívico e de responsabilidade, integrar redes globais de investigação científica e de conhecimento, construir áreas de conhecimento partilhado e contribuir para o desenvolvimento do futuro e ser importantes agentes de mudança e de transformação, nomeadamente na área da saúde.

E a responsabilidade social nos hospitais?

Muitos hospitais públicos e privados assumiram o compromisso de responsabilidade social, baseado na transparência da sua atividade e na conciliação entre a prestação de cuidados e o envolvimento, motivação e satisfação de todos os intervenientes – colaboradores, utentes/doentes e familiares, fornecedores e acionistas (no caso dos privados) e referem ter várias iniciativas de responsabilidade social com preocupação de inserir e apoiar a formação dos seus colaboradores e referem contribuir para uma sociedade mais saudável e solidária com aqueles que, por alguma razão, estão mais fragilizados.

Haverá alguma distância entre o que escrevem, o que ensinam, e o que praticam? O fundamental é que responsabilidade social e ética não sejam apenas discursos ou boas intenções, mas que confi-

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gurem ações concretas, imprimindo coerência entre discurso e ação.

É num quadro de grande exigência em termos de acesso universal e equitativo aos cuidados de saúde, necessitando da conciliação das preocupações inerentes aos recursos existentes, à tecnologia e aos valores humanos no interior das estratégias da gestão, que urge discutir a responsabilidade social também no setor da saúde (público e privado), não esquecendo as intervenções de prevenção nas estratégias e políticas de saúde pública, face às as intervenções apenas de tratamentos. Ou seja, implementar eficazmente a adoção de estilos de vida saudáveis, nomeadamente nos hábitos alimentares e de exercício físico, num quadro geral de individualização da responsabilidade pelos riscos de saúde associados aos estilos de vida ao longo do curso de vida, junto das populações que as instituições servem. Nesta perspetiva, os profissionais de saúde deveriam trabalhar em conjunto com outros segmentos da sociedade na antecipação e na colmatação dos fatores geradores de impactes negativos.

E a responsabilidade social nas sociedades científicas?

A função das universidades e dos hospitais (e dos programas de internato médico) não deve ser apenas o compromisso de formar pessoas com as competências técnicas necessárias para atender às exigências do campo profissional, mas formar pessoas com a competência de pensar criticamente sobre a realidade que as circunda; o mesmo se deve aplicar às sociedades científicas que devem estar alertas ao crescente número de problemas no mundo. A Sociedade Europeia de Endocrinologia redigiu o primeiro *White Paper* e elencou como os Endocrinologistas podem contribuir para uma Europa Mais Saudável e mais sustentável e foram identificadas quatro principais áreas de política:1) Obesidade; 2) Doenças endócrinas raras; 3) Cancro e Endocrinologia; 4) Disruptores endócrinos.

Em Portugal, o facto de já existirem vários programas nos planos da Direção Geral de Saúde não garante a sua execução. De facto, existem os programas "Promoção da Alimentação Saudável" e "Promoção da Atividade Física", e também a resolução da Assembleia da República nº 195/2021, em que recomenda ao Governo vinte e três medidas de prevenção, tratamento e combate à obesidade.

É necessário elaborar planos de ação, alocar a cada ação recursos, atribuir um responsável pela sua realização, definir um limite temporal para seu términus, e associar medidas para aferir a sua eficácia. As sociedades científicas podem ter um papel de pressão para o cumprimento destes planos já que visam contribuir para uma população mais saudável e maior sustentabilidade.

Em conclusão, universidades, hospitais e sociedades cientificas não se devem contentar em apenas transmitir ciência, mas em criar ciência através da indissociabilidade ensino e investigação cientifica; incorporar um sentido para a formação de estudantes, de especialistas e constante atualização dos médicos, e devem manter-se abertas ao contexto social, económico e profissional e nunca se fecharem em si mesmas; sendo essencial a difusão do conhecimento produzido e não devem esquecer os objetivos relacionados com a responsabilidade social, inclusivamente dos próprios intervenientes.

Desejo a todos os Colegas um Excelente 2023.

Responsabilidades Éticas

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Artigo Original

Impact of COVID-19 in New-Onset Type 1 Diabetes Mellitus in a Large Portuguese Pediatric Diabetes Center

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Criança;
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SARS-CoV-2.

A B S T R A C T

Introduction: Our aim was to characterize new-onset type 1 diabetes mellitus (T1D) cases in a pediatric population referred to a large pediatric diabetic center throughout the first year of the COVID-19 pandemic, comparing it to previous years.
Methods: Retrospective study including patients under 18 years with new-onset T1D, from March 12th 2020 to March 11th 2021. A control group was defined using data on patients under 18 years with new-onset T1D referred to the same hospital in the 3 previous years (from March 2017 to March 2020). Data was analyzed using SPSS. A *p* value of 0.05 was used as threshold of significance.
Results: Between March 12th 2020 and March 12th 2021, 44 patients were diagnosed with new-onset T1D. The control group included 96 patients, resulting in an incidence of 32 cases/year (37.5% rise). January 2021 was the month with the higher number of diagnosis, corresponding to the peak of novel SARS-CoV-2 infections. During the pandemic, new-onset T1D cases in children under 2 years-old doubled, when comparing to mean incidence in previous years. Median delay to diagnosis was not significantly different from previous years. Diabetic ketoacidosis (DKA) at presentation was present in 50% of cases that were diagnosed after lockdown, increasing substantially from previous years (38.5%). DKA's severity was also significantly higher (40.9%, p=0.04), as were Intensive Care Unit admission (13.6%, p=0.04).
Conclusion: Despite the existance of molecular pathways that could lead to islet cell injury, the role of the new coronavirus in the pathogenesis of DKA and T1D onset is still unclear. Disease severity could also be related to a higher proportion of younger children.

Impacto da COVID-19 na Diabetes Mellitus Inaugural num Centro de Diabetologia Pediátrica Portuguesa

R E S U M O

Introdução: O nosso objetivo foi caracterizar os casos de diabetes *mellitus* tipo 1 (T1D) inaugurais na população pediátrica referenciada a um centro de diabetes pediátrica durante o primeiro ano da pandemia por COVID-19, comparando-os com os anos anteriores.
Métodos: Estudo retrospectivo incluindo doentes com menos de 18 anos com T1D inaugural, de 12 de Março de 2020 a 11 de Março de 2021. Foi definido um grupo de controlo a partir de dados de doentes com menos de 18 anos com T1D inaugural referenciados ao mesmo hospital nos 3 anos anteriores (de Março de 2017 a Março de 2020). Os dados foram analisados utilizando SPSS. Foi utilizado um valor *p* de 0,05 como limiar de significância.

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Resultados: Entre 12 de Março de 2020 e 12 de Março de 2021, foram diagnosticados 44 doentes com T1D. O grupo de controlo incluiu 96 pacientes, com incidência de 32 casos/ano (aumento de 37,5%). Janeiro de 2021 foi o mês com o maior número de diagnósticos, correspondendo ao pico das novas infecções por SARS-CoV-2. Durante a pandemia, os casos de T1D em crianças com menos de 2 anos duplicaram quando comparados com a incidência média nos anos anteriores. O atraso médio no diagnóstico não foi significativamente diferente dos anos anteriores. A cetoacidose (CAD) como forma de apresentação ocorreu em 50% dos casos diagnosticados após o decretar de confinamento, aumentando substancialmente em relação aos anos anteriores (38,5%). A gravidade da CAD foi também significativamente maior (40,9%, p=0,04), tal como a admissão na Unidade de Cuidados Intensivos (13,6%, p=0,04).

Conclusão: Apesar da existência de mecanismos moleculares comuns que poderiam conduzir a lesão do tecido pancreático, o papel entre o papel do novo coronavírus na patogénese da T1D inaugural é ainda incerto. A maior gravidade da CAD poderá também estar relacionado com uma maior proporção de casos em crianças mais novas.

Introduction

December 2019 marked the unsuspicious beginning of a global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Since then, SARS-CoV-2 associated disease (COVID-19) has caused a profound shift in countless aspects of society. One of these aspects was healthcare access, both emergent and routine,[2] giving way to concerns that delayed referral to healthcare could promote increased severity of non-COVID-19 related diseases.[3,4] Simultaneously, SARS-CoV-2 has been increasingly recognized as a potent inflammatory trigger, prompting immune deregulation through mechanisms such as molecular mimicry and "cytokine storms," the most striking pediatric example being the multisystem inflammatory syndrome in children (MIS-C).[5,6]

Previous publications have highlighted a seeming rise in type 1 diabetes mellitus (T1D) diagnosis, as well as increased severity for new-onset T1D.[7] Higher risk for diabetic ketoacidosis (DKA) in patients with known T1D has also been reported.[8] Both delayed access to healthcare and SARS-CoV-2 immunogenicity have been enlisted as possible explanations for these findings.[9,10]

We aimed to further contribute to this discussion, by characterizing new-onset T1D cases in a pediatric population referred to a large pediatric diabetic center throughout the first year of the COVID-19 pandemic, comparing it to previous years, namely in demographic characteristics, clinical and biochemical presentation, as well as DKA's incidence and severity.

Methods

A retrospective study performed in a Pediatric Endocrinology Unit of a level III hospital was performed, including children and adolescents under 18 years with new-onset T1D, from March 12th 2020 (time of the first lockdown imposition in Portugal) to March 11th 2021 (12 months duration). For the control group, clinical, epidemiological and laboratorial data on children and adolescents under 18 years with new-onset T1D referred to the same hospital in the 3 previous years (from March 2017 to March 2020) was collected.

T1D was established based on the usual diagnostic criteria.[11] Patients with incomplete information regarding presentation status were excluded from the study.

Data was collected from electronical clinical files and included: age at presentation; gender; co-morbidities; family history of T1D, type 2 diabetes mellitus (T2D), or other autoimmune disease; symptoms and their duration; blood glucose, ketonemia, pH, bicarbonate and HbA1C at presentation; SARS-CoV-2 protein chain reaction (PCR) status; type of hospitalization (ward/Paediatric Intensive Care Unit, PICU).

Clinical presentation of T1D was categorized as: hyperglycemia, hyperglycemia with ketonemia (≥0.6 mmol/L), and DKA. DKA was classified as: mild (pH <7.3 and/or bicarbonate <15 mmol/L), moderate (pH <7.2 and/or bicarbonate <10 mmol/L), and severe (pH <7.1 and/or bicarbonate <5 mmol/L).

Data was analyzed using SPSS, 21th version software (SPSS, Chicago, IL) for Mac. Continuous data were compared by use of paired and unpaired Student t test whenever applicable. Independent proportions were compared by use of the 2-tailed Fisher exact test. A p value of 0.05 was used as the threshold of significance. Results are presented as median (min., max.) unless stated otherwise.

Results

Incidence

Our study included 140 patients with new-onset T1D, 44 of which diagnosed between March 12th 2020 and March 12th 2021. The control group was composed of 96 patients who were diagnosed between March 12th 2017 and March 11th 2020, resulting in an incidence of 32 cases/year. This reflected a 37.5% rise in new-onset T1D cases.

While in previous years, a mean incidence of 2.7 cases/month was observed, during the pandemic period, the monthly incidence of new T1D cases exceeded this figure in most months, with a mean of 3.6 new cases/month. In the group of patients diagnosed during the COVID-19 pandemic, the number of T1D diagnosis steadily increased until September, with January 2021 being the month with the higher number of diagnosis (8 cases), doubling the mean monthly incidence that year. January 2021 also corresponds to the peak of novel SARS-CoV-2 infections in the country. The annual distribution of T1D cases can be appreciated in Fig. 1, whereas the incidence of new SARS-CoV-2 cases can be found in Fig. 2.

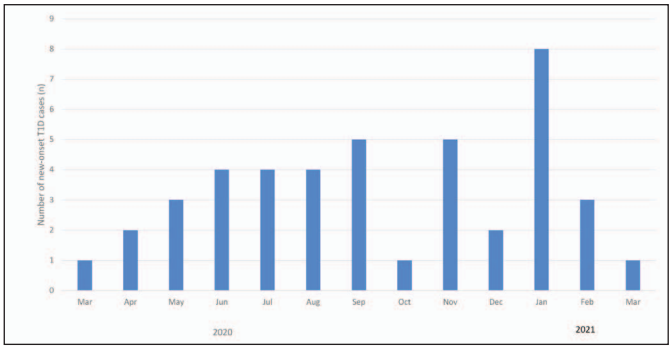

Figure 1. Annual distribution of new-onset T1D cases between 2020 and 2021.

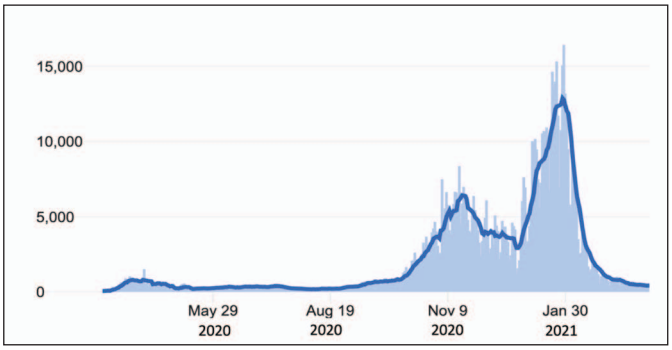

Figure 2. Incidence of SARS CoV-2 infections in Portugal (Data from Center for Systems Science and Engineering at Johns Hopkins University)

Demographic characteristics

Patients diagnosed during the pandemic had a median age of 9 years (+/- 4.2, min. 0.5, max. 15.8 years), whilst patients in the control group had a median age of 10.7 years (+/- 4.5, min. 0.9, max. 17.9 years). This difference did not reach statistical significancy. Overall, the incidence of new-onset T1D increased both in the group of patients aged less than 10 years (22 cases *vs* 15.7/year in the control group) and of those aged 10 years or more (22 cases *vs* 16.7/year in the control group). Peak incidence was observed in the group of patients aged 10 to 14 years in both groups (43.2% *vs* 41.7% in the control group). From March 2020 on, new-onset T1D cases in children under 2 years-old doubled (2 cases), when comparing to mean incidence in previous years (1 case/year).

Gender distribution was similar in the two groups, with a slight male predominance of cases (52.3% *vs* 53.1% in the control group) (Table 1).

Table 1. Demographic characteristic of both groups

	COVID group	Control group	Significance
No.	44	96	-
Gender, no. (%)			
Female	21 (47.7)	45 (46.9)	NS
Male	23 (53.2)	51 (53.1)	NS
Age group, no. (%)			
< 2	2 (4.5)	3 (3.1)	NS
≥ 2-5	5 (11.4)	19 (16.7)	NS
≥ 5-10	15 (34.1)	25 (27.1)	NS
≥ 10-15	19 (43.2)	40 (42.7)	NS
≥ 15	3 (6.8)	10 (10.4)	NS

NS: non significant.

Family history of autoimmune diseases was present in 50% of the cases in the control group, while being slightly less prevalent (43.2%) in the cases diagnosed during the pandemic. T1D familial history was present in 27.3% of cases during the pandemic and in 15.6% in the previous years.

Clinical characteristics

The duration of symptoms was of 2 to 4 weeks, identical before and after lockdown imposition (29.2% and 31.7% respectively). However, the number of patients presenting with symptoms for less than a week was much higher in the pandemic group compared to the control group (20.5% *vs* 9.4%, not statistically significant).

There were no statistically significant differences between presenting symptoms before and after the pandemic. Polydipsia was the most frequent symptom (88.5% and 84.1% respectively), followed by polyuria (82.3% and 75% respectively) and weight loss (72.9% and 61.4% respectively).

DKA at presentation was present in the majority (50%) of cases that were diagnosed after lockdown, increasing substantially from previous years (38.5%) (Fig. 3). DKA's severity also augmented in a statistically significant manner (40.9% of DKA cases vs 18.9% in previous years, p=0.04).

PICU admissions were also significatively higher: 13.6% subjects required admission to the PICU during the pandemic, compared to just 4.2% in prior years (p=0.04) (Fig. 4).

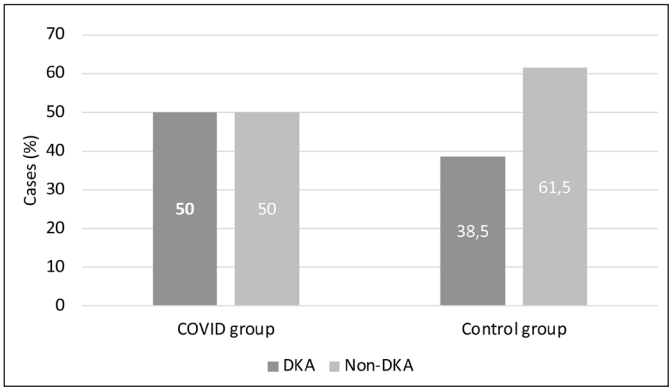

Figure 3. Proportion of DKA and non-DKA presentation in patients during the pandemic, comparing to the control group.

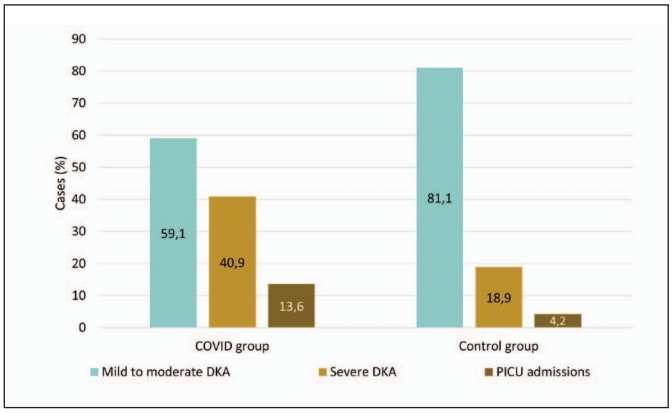

Figure 4. Severity and PICU admissions comparison between T1D cases diagnosed during the pandemic, compared to the control group.

Biochemical characteristics

Mean A1C hemoglobin was of 11.2% (+/- 3.2%) during the pandemic, slightly lower than in previous years (11.4% +/- 2.9%), although this finding was not statistically significative.

COVID-19 infection

Since the beginning of the pandemic period, all patients were tested for SARS-CoV-2 via a PCR test, as this was routine for patients admitted to our center's infirmaries. Only 2 patients had a positive PCR test for SARS-CoV-2: an 8-year boy who presented with mild DKA, and a 13-year old adolescent, presenting with moderate DKA.

Serologies for SARS-CoV-2 were not performed regularly on

the patients diagnosed initially, as the technology was not available.

Discussion

A higher number of pediatric new-onset T1D cases was observed during the first year of COVID-19 in our center compared to previous years. The cases' severity was also significantly higher, with a substantial rate of PICU admissions. Various factors could have contributed to this finding. The hypothesis that delayed access to healthcare facilities, as it was seen with other pathologies[3,4] could have taken a part in exponentiating DKA severity was not sustained by our data, as the average delay to diagnosis was not significantly different from previous years. Nevertheless, and albeit not statistically significant, a higher number of patients presented to the emergency room with short-lasting symptoms, a finding that remains unexplained.

A possible role of viral infections in T1D onset has been postulated for over 40 years.[12-14] Rotavirus and enterovirus have frequently been proposed as likely culprits, although not exclusively – in 2009, during the aftermath of the SARS-CoV-1 pandemic, it was suggested that coronavirus used angiotensin converting enzyme 2 (ACE2), as the cellular entry point in pancreatic islet cells.[15-17] A similar pathway was proposed for SARS-CoV-2 after the publication of several case series where a high prevalence of hyperglycemia was observed in adult patients that could not be fully explained by corticoid therapy and the viral infection itself; this fact imposed an extra risk for adverse outcomes.[18-20] In addition to ACE2 receptors, interleukin-6 has also been thought to play a role in cytokine-mediated pancreatic damage, since it is one of the main molecules involved in both Th1 autoimmune islet cell destruction seen in T1D and COVID-19-related cytokine storms.[21-23] The finding that the months when more T1D cases were diagnosed paralleled the period when more SARS-CoV-2 infections were diagnosed in Portugal, creating somewhat overlapping graphs (Figs. 1 and 2, respectively), could further support this hypothesis.

The higher overall severity of DKA could also be partially explained by the higher number of cases in children under 5 years old, which has been identified as a risk factor by recent studies.[24-26] In another recently published study, we have observed a higher incidence of DKA in younger ages.[27] Previous studies have additionally shown increasing trends for new-onset T1D cases in this age group.[28,29] Reasons for this include a lower index of suspicion and possibly a more aggressive inflammatory islet cell destruction, in line with recent findings that a specific type 1 endotype may exist in this age group.[30,31]

The variation trends of new onset T1D cases have been studied for multiple decades, with reported peak incidence cyclicity of 4 to 6 years.[32] No clear rationale has been stablished, although viral epidemics have been previously implicated in season variations of T1D incidence.[33] The possibility that we are heading towards a new high-incidence period, and the contribution of present-day viral pandemics to such pattern variability, namely COVID-19, can only be guessed at the present time.

Limitations

We find that the small cohort of this study was the main limitation, constraining its power. A multicentric approach would help minoring this aspect. Serological SARS-CoV-2 tests were not performed routinely during the first months of the pandemic, which could have supported the link between infection and T1D onset, even though causality would always be hard to stablish with a retrospective study.

Conclusion

Upon the emergence of the SARS-CoV-2 pandemic, we found a higher number of T1D cases, as well as more frequent and more severe DKA. Longer delay to diagnosis did not seem to significantly contribute to this finding. Despite the existance of molecular pathways that could lead to islet cell injury, the role of the new coronavirus in the pathogenesis of DKA and T1D onset is still unclear. Disease severity could also be related to a higher proportion of younger children. Broader studies are lacking for more definitive conclusions to be drawn.

Contributorship Statement / Declaração de Contribuição:

FBC, AL, CR, SB and AMG collected the data.
FBC analyzed the data and wrote the manuscript.
CD, ALF, JG, RP, LL and CL revised and approved the final manuscript.

Responsabilidades Éticas

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References / Referências

1. Carvalho T, Krammer F, Iwasaki A. The first 12 months of COVID-19: a timeline of immunological insights. Immunology. 2021;21:245-56. doi: 10.1038/s41577-021-00522-1.

2. Czeisler MÉ, Marynak K, Clarke KE, Salah Z, Shakya I, Thierry JM, et al. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1250-7. doi: 10.15585/mmwr.mm6936a4.
3. Jeffery M, D'Onofrio G, Paek H, Platts-Mills TF, Soares WE 3rd, Hoppe JA, et al. Trends in Emergency Department Visits and Hospital Admissions in Health Care Systems in 5 States in the First Months of the COVID-19 Pandemic in the US. JAMA Intern Med. 2020;180:1328-33. doi: 10.1001/jamainternmed.2020.3288.
4. Almeida A, Santo T, Mello M, Cedro AV, Lopes NL, Ribeiro AP, et al. Repercussions of the COVID-19 Pandemic on the Care Practices of a Tertiary Hospital. Arq Bras Cardiol. 2020;115:862-70. doi: 10.36660/abc.20200436.
5. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell. 2020;183:968-981.e7. doi: 10.1016/j.cell.2020.09.016.
6. Gupta M, Weaver DF. COVID-19 as a trigger of brain autoimmunity. ACS Chem Neurosci. 2021;12:2558-61. doi: 10.1021/acschemneuro.1c00403.
7. Unsworth R, Wallace S, Oliver NS, Yeung S, Kshirsagar A, Naidu H, et al. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. Diabetes Care. 2020;43:e170-1. doi: 10.2337/dc20-1551.
8. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab. 2020;22:1935-41. doi: 10.1111/dom.14057.
9. Nat Metab. 2021;3:123-25. doi: 10.1038/s42255-020-00339-7.
10. International Society for Pediatric and Adolescent Diabetes (ISPAD). Summary of recommendations regarding COVID-19 in children with diabetes: Keep Calm and Mind your Diabetes Care and Public Health Advice. Pediatr Diabetes. 2020;21:413-4. doi: 10.1111/pedi.13013.
11. Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes. 2018;19 Suppl 27:7-19. doi: 10.1111/pedi.12773.
12. Yoon J, Austin M, Ondera T, Notkins AL. Virus-induced diabetes mellitus – isolation of a virus from the pancreas of a child with diabetic ketoacidosis. N Engl J Med. 1979;300:1173-9. doi: 10.1056/NEJM197905243002102.
13. Yoon J, Jun H. The role of viruses in Type I diabetes: two distinct cellular and molecular pathogenic mechanisms of virus-induced diabetes in animals. Diabetologia. 2001;41:271-85.
14. Olstone M. Virus infection triggers insulin- dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. Cell. 1995;7:319-31.
15. Clements G, Galbraith D, Taylor K. Coxsackie B virus infection and onset of childhood diabetes. Lancet.1995;346:221-3.
16. Harrison LC, Perrett KP, Jachno K, Nolan TM, Honeyman MC. Does rotavirus turn on type 1 diabetes? PLoS Pathog. 2019;15:e1007965. doi: 10.1371/journal.ppat.1007965.
17. Yang J, Lin S, Ji X, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47:193–9. doi: 10.1007/s00592-009-0109-4.
18. Ebekozien O, Noor N, Gallagher M, Alonso GT. Type 1 Diabetes and COVID-19: Preliminary Findings From a Multicenter Surveillance Study in the U.S. Diabetes Care. 2020;43: e83-5. doi: 10.2337/dc20-1088.
19. Ilias I, Zabuliene L. Hyperglycemia and the novel Covid-19 infection: Possible pathophysiologic mechanisms. Med Hypotheses. 2020;139:109699. doi: 10.1016/j.mehy.2020.109699.
20. Caballero A, Ceriello A, Misra A, et al. Hyperglycemia and COVID-19: What was known and what is really new? Diabetes Res Clin Pract. 2020;167:108383. doi: 10.1016/j.diabres.2020.108383.
21. Sathish T, Tapp R, Cooper M. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. Diabetes Metab. 2021;47 :101204. doi: 10.1016/j.diabet.2020.10.002.
22. Gentile S, Strollo F, Mambro A, Ceriello A. COVID-19, ketoacidosis and new-onset diabetes: Are there possible cause and effect relationships among them? Diabetes Obes Metab. 2020;22:2507–8. doi: 10.1111/dom.14170.
23. Buggs-Saxton C. Care of pediatric patients with diabetes during the coronavirus disease 2019 (COVID-19) pandemic. Pediatr Clin N Am. 2021;68:1093-101. doi: 10.1016/j.pcl.2021.05.014.
24. B factors. A twenty- year experience in a tertiary Belgian centre. Pediatr Diabetes. 2019;20:584-93
25. Szypowska A, Dżygało K, Wysocka-Mincewicz M, Mazur A, Lisowicz L, Ben-Skowronek I, et al. High incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes among Polish children aged 10-12 and under 5 years of age: A multicenter study. Pediatr Diabetes. 2017;18:722-8. doi: 10.1111/pedi.12446.
26. Chobot A, Polanska J, Brandt A, Deja G, Glowinska-Olszewska B, Pilecki O, et al. Updated 24-year trend of Type 1 diabetes incidence in children in Poland reveals a sinusoidal pattern and sustained increase. Diabetic Medecine. 2017;34:1252-8. doi: 10.1111/dme.13345.
27. Branco Caetano F, Lança A, Rodrigues C, Garcia AM, Bota S, Diamantino C, et al. Stable rates of diabetic ketoacidosis at the initial episode of type 1 diabetes mellitus are associated with a shift towards younger age at diagnosis: 8 years' experience of a large Portuguese centre. Int J Community Med Public Health. 2022;96):2402-.7
28. Samuelsson U, Stenhammar L. Clinical characteristics at onset of Type 1 diabetes in children diagnosed between 1977 and 2001 in the south-east region of Sweden. Diabetes Res Clin Pract. 2005;68:49–55.
29. Geyikli İ, Keskin M, Kör Y, Akan M. increased resistin serum concentrations in patients with type 1 diabetes mellitus. J Clin Res Pediatr Endocrinol. 2013;5:189–93. doi: 10.4274/Jcrpe.1072.
30. Leete P, Willcox A, Krogvold L, Dahl-Jørgensen K, Foulis AK, Richardson SJ, et al. Differential Insulitic Profiles Determine the Extent of β-Cell Destruction and the Age at Onset of Type 1 Diabetes. Diabetes. 2016;65:1362-9. doi: 10.2337/db15-1615.
31. Battaglia M, Ahmed S, Anderson M, Atkinson MA, Becker D, Bingley PJ, et al. Introducing the Endotype Concept to Address the Challenge of Disease Heterogeneity in Type 1 Diabetes. Diabetes Care. 2020;43:5-12. doi: 10.2337/dc19-0880.
32. Patterson C, Harjutsalo V, Rosenbauer J, Neu A, Cinek O, Skrivarhaug T, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. Diabetologia. 2019;62:408-17. doi: 10.1007/s00125-018-4763-3.
33. Ruiz PL, Tapia G, Bakken IJ, Håberg SE, Hungnes O, Gulseth HL, et al. Pandemic influenza and subsequent risk of type 1 diabetes: a nationwide cohort study. Diabetologia. 2018;61:1996-2004. doi: 10.1007/s00125-018-4662-7.

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Artigo Original

Use of SGLT2 Inhibitors in Type 1 Diabetes: Experience from a Portuguese Tertiary Center

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A B S T R A C T

Introduction: Basal-bolus insulin management remains the only option for effective treatment of type 1 diabetes (T1DM). However, most of T1DM patients do not achieve glycemic targets and so there has been a great interest in adjunct therapies, as the use of SGLT2 inhibitors (SGLT2i). Our study aimed to assess the impact of introducing an SGLT2i on glycemic control, weight, and insulin doses in a group of T1DM patients.
Methods: A retrospective longitudinal study was conducted in the Endocrinology Department of a University Hospital. Inclusion criteria comprised T1DM patients, under intensive basal-bolus insulin therapy (continuous subcutaneous insulin infusion-CSII, or multiple daily injection), who initiated therapy with an SGLT2i and with regular use of freestyle libre®. CGM metrics, daily insulin dose, glucose levels, body weight, and body mass index were evaluated, using the ambulatory glucose profile (AGP), Libreview®, and patients' clinical records, before and after 3 months of dapagliflozin introduction. Statistical analysis was performed using IBM SPSS Statistics v.26 for Windows.
Results: 17 patients were included with a mean age of 36.12 years (SD=11.061), 58.82% female, 64.71% under CSII and 35.293% under multiple daily injection. After the introduction of dapagliflozin, there was an overall improvement in glycemic control, with statistically significant differences in the following parameters: %time in range (50.9% to 60.2%; p=0.019); coefficient of variation (43.7±6.2% to 40.7 ±6.4%; p=0.001); GMI (7.6% to 7.0%; p=0.001); total insulin daily dose (53.9 U to 44.0 U; p=0.001); basal insulin dose (30.0U to 25.0U; p=0.001); prandial insulin dose (24.7 to 20.0U; p=0.028). At the same time, median fasting glucose, pre and post-lunch and pre-dinner glucose were significantly reduced, as well as body weight and BMI. Regarding the difference of glucose levels with and without dapagliflozin in the various periods of the day, the median was higher at post-lunch period (-35.45 mg/dL IQR: -44.0, -10.22) and lower at post-dinner time (-6.31 mg/dL, IQR: -46.78, 2.105).
Conclusion: The introduction of SGLT2i in this population improved glycemic control during pre and postprandial periods. The maximal effect was observed in post-lunch period, possibly because of the therapeutic prescription schedule.

Palavras-chave:
Diabetes Mellitus Tipo 1/tratamento farmacológico;
Inibidores do Transportador 2 de Sódio-Glicose/uso terapêutico.

Uso de Inibidores SGLT2 na Diabetes Tipo 1: Experiência de um Centro Terciário Português

R E S U M O

Introdução: A utilização de insulina em regime basal/bolus constitui atualmente a única terapêutica efetiva para a diabetes *mellitus* (DM) tipo 1. Contudo, a maioria dos doentes não atinge os alvos glicémicos, havendo um crescente interesse na utilização de fármacos coadjuvantes. A utilização dos inibidores SGLT2 (SGLT2i) tem merecido especial atenção. O nosso estudo teve como objetivo avaliar o impacto da sua introdução no controlo glicémico, no peso e nas doses de insulina num grupo de doentes com DM tipo 1.

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Métodos: Estudo longitudinal retrospetivo que incluiu diabéticos tipo 1, sob insulinoterapia intensiva (perfusão subcutânea contínua de insulina – PSCI ou múltiplas administrações diárias), e com uso regular de freestyle libre®, em quem foi iniciada terapêutica com SGLT2i. Foram considerados os dados relativos às métricas da monitorização contínua de glicose, dose diária de insulina, níveis de glicose, peso corporal e IMC. Avaliados os dados constantes no processo clínico e no ambulatory glucose profile (AGP) e Libreview®, antes e após 3 meses da introdução da dapagliflozina. A análise estatística foi desenvolvida através do SPSS Statistics v.26.
Resultados: Foram incluídos 17 doentes com uma média de idades de 36,12 anos (DP=11,061), 58,82% do sexo feminino, 64,71% sob PSCI e 35,293% sob múltiplas administrações. Após introdução da dapagliflozina, verificou-se uma melhoria global do controlo glicémico, com diferenças estatisticamente significativas nos seguintes parâmetros: %tempo no alvo (50,9% *vs* 60,2%; *p*=0,019); coeficiente de variação (43,7±6,2% *vs* 40,7 ±6,4%; *p*=0,001); GMI (7,6% *vs* 7.0%; *p*=0,001); dose diária total (53,9 U *vs* 44,0 U; *p*=0,001); dose de insulina basal (30,0U *vs* 25,0U; *p*=0,001) e dose de insulina prandial (24,7U *vs* 20,0U; *p*=0,028). As medianas da glicemia do jejum, glicemia pré e pós-almoço e pré-jantar reduziram significativamente, assim como o peso e o IMC. Em relação às diferenças nos níveis de glicose antes e depois da dapagliflozina nos vários períodos do dia, a mediana foi maior no período pós-almoço (-35,45 mg/dL AIQ: -44,0; -10,22) e menor no período pós-jantar (-6,31 mg/dL, AIQ: -46,78; 2,105).
Conclusão: A introdução da dapagliflozina melhorou o controlo glicémico, cobrindo os períodos pré e pós-prandiais. O efeito máximo foi observado no período após o almoço, o que poderá associar-se à posologia utilizada.

Introduction

Glycemic control in people with type 1 diabetes (T1DM) reduces the risk of microvascular and macrovascular complications.[1] The mainstay of treatment requires the administration of both basal and prandial insulin, trying to mimic the physiologic secretion of insulin. Basal-bolus insulin management remains the only option for effective treatment of type 1 diabetes.

Despite the recent exponential improvement in therapeutic approaches, namely the use of insulin pumps, continuous glucose monitoring (CGM) and hybrid closed-loop systems, the risk of hypoglycemia and weight gain associated with insulin still exist, and the latter are barriers to optimal use of insulin therapy. As a consequence, most of T1DM patients do not achieve glycemic targets.[2]

In this context, there has been a great interest in adjunct therapies for T1DM to help improving glycemic control.[2] The majority of noninsulin therapies approved for type 2 diabetes are not effective in T1DM. Recently, a new approach was performed, using sodium–glucose cotransporter (SGLT) inhibitors as an adjunct to insulin therapy in T1DM.[3] This pharmacological class blocks SGLT type 1 transporter in the intestinal tract, delaying dietary glucose absorption (SGLT1 inhibitors),[4] and blocks SGLT type 2 transporter in the proximal tubule of the kidney resulting in glycosuria and natriuresis (SGLT2 inhibitors). SGLT inhibitors act independently of insulin to facilitate the improvement of glycemic control without exacerbating insulin adverse effects, such as hypoglycemia and weight gain.[3]

Initially used off-label, dapagliflozin, an SGLT2 inhibitor, received the approval by EMA for its use as adjunctive therapy in T1DM patients, in 2019.[5] Oral dapagliflozin was then approved in the EU at a dosage of 5 mg/day as an adjunct to insulin in adults with type 1 diabetes (T1DM) and a body mass index (BMI) of≥27 kg/m^2, when insulin alone does not provide adequate glycemic control despite optimal insulin therapy. In the phase III DEPICT-1[6] and -2[7] trials, use of dapagliflozin 5 mg/day as an adjunct to insulin improved glycemic control and reduced total daily insulin dose and body weight relative to placebo in adults with inadequately controlled T1DM, over 24 weeks of treatment. Dapagliflozin was generally well tolerated with a good safety profile and a hypoglycemia profile generally similar to placebo.[8] However, higher frequency of diabetic ketoacidosis (DKA) was consistently reported in patients with type 1 diabetes, and specific risk minimization measures to health care providers and patients were recommended by EMA. Similar results were obtained in inTandem clinical trial that assessed efficacy and safety of sotagliflozin combined with insulin therapy for the treatment of patients with T1DM.[9,10] and in the EASE clinical trial that tested empagliflozin.[11] Recently, the indication for dapagliflozin use in type 1 diabetes was withdrawn by the pharmaceutical company.[12]

Apart from DKA, the use of this drug class has other potential associated adverse effects, so it is mandatory to increase the knowledge and to recognize the best criteria that allow the optimal use in T1DM.

The present work aimed to assess the impact of introducing an SGLT2i on glycemic control, weight and insulin doses in a group of patients with T1DM.

Material and Methods

A retrospective longitudinal study was conducted in people with type 1 diabetes followed in the Endocrinology Department of a University Hospital. Inclusion criteria comprised T1DM patients under intensive basal-bolus insulin therapy (continuous subcutaneous insulin infusion-CSII, or multiple daily injection - MDI) who initiated therapy with an SGLT2i (dapagliflozin 10 mg once a day, dapagliflozin 10mg ½ pill once a day, or the association dapagliflozin/metformin 5/850 mg once a day). Regular use of freestyle libre®, considered as at least 70% of time CGM is active in the last 14 days, was also an inclusion criteria. The exclusion criteria comprised people under 18 years, pregnant women, body mass index (BMI) <27 kg/m^2, evidence of insulin omissions (in non-adherent patients), insulin exchanges, and patients who were prescribed with new drugs with potential effects on glycemia and weight during study period. Patients with history of pancreatic disorders resulting in decreased β-cell function, signs of poorly controlled diabetes (including DKA requiring medical intervention or hospitalization for hyperglycemia or hypoglycemia in the previous month), and unstable renal disease were also excluded.

Patients' clinical records were appraised to evaluate sociodemographic data and the following clinical information at baseline: duration of type 1 diabetes; method of insulin delivery; mean total insulin dose; mean body weight/BMI; estimated glomerular filtration rate (eGFR). The presence of diabetic nephropathy (defined as the presence of urinary albumin ≥300 mg/g creatinine and/or

an estimated glomerular filtration rate <60 mL/min/1.73 m^2), diabetic retinopathy (defined as the diagnosis of nonproliferative or proliferative retinopathy by an experienced ophthalmologist) and diabetic neuropathy (presence of distal symmetric polyneuropathy or autonomic neuropathy) were also assessed, as well as the existence of previous macrovascular complications (stroke, myocardial infarction and peripheral artery disease).

The following data were assessed, before and after 3 months of treatment, using the ambulatory glucose profile (AGP) from the previous 14 days and other glucose data from libreview® platform: glucose management indicator (GMI); coefficient of variation (CV); percentage and mean value of time in range, defined as glucose levels between 70 and 180 mg/dL (%TIR); percentage and mean value of time above range, defined as glucose levels > 180 mg/dL (%TAR); percentage and mean value of time below range, defined as glucose levels <70 mg/dL (%TBR). Levels of fasting glucose, pre-meal glucose (lunch and dinner), 2 hours post-meal glucose (lunch and dinner), and postprandial glucose excursion (lunch and dinner) were assessed using the glucose values available in the section "transfer glucose data" of the Libreview platform. Total daily insulin dose (TDD), basal dose, prandial dose, body weight and BMI were also evaluated.

The occurrence of genital infections, severe hypoglycemia (level 3 hypoglycemia) and DKA were also registered.

Statistical analysis was performed using IBM SPSS Statistics v.26 for Windows.

To characterize the study population, means with standard deviations (SD) or medians with interquartile ranges (IQR) were calculated for continuous data. For categorical variables, the absolute numbers and percentage proportions were used. The Shapiro–Wilk (SW) and Kolmogorov-Smirnova tests were used to assess the normality of data.

Differences between groups were evaluated using the non-parametric paired test Wilcoxon signed-rank or paired sample t-test. *p* values lower than 0.05 were considered as significant.

Results

The study included 17 patients with a mean age of 36.12 years (SD =11.06) ranging from 22 to 61 years. A percentage of 58.82% of the population were female. Baseline characteristics of included patients are discriminated in Table 1.

The patients included had a mean duration of T1DM of 17.65 (±9.50) years and the majority (64.7%) was under CSII. Regarding body weight and BMI, the mean was 88.71 kg and 30.79 kg/m^2, respectively.

In what concerns to eGFR, the mean was 96.96 mL/min/1.73 m^2, compatible with normal kidney function.

After the introduction of dapagliflozin, there was an overall improvement in glycemic control.

Statistical difference was found in TIR after 3 months of the introduction of the drug, increasing from 50.9% to 60.2% (*p*=0.019), reflecting an additional 2.78 hours of time spent in range every day (*p*=0.006). Both the CV and GMI decreased significantly from 43.7±6.2% to 40.7 ±6.4% (*p*=0.001) and 7.6% (7.2-9.2) to 7% (6.7-7.5) (*p*=0.001), respectively (Table 2).

The median of fasting glucose 3 months after the introduction of dapagliflozin decreased from 161.9 to 144.9 (*p*=0.023), as well as the levels of pre-meal glucose at lunch and dinner and post-meal glucose at lunch, that reduced significantly (Table 3). A reduction in %TAR was also found, although with no statistical significance (41.5% to 32.2%, *p*=0.058). Similarly, there was a mean reduction of 2.15 hours of time spent above range (*p*=0.063). In what concerns to TBR, there was no statistical difference after the use of this SGLT2i.

In relation to the difference of glucose levels with and without dapagliflozin in the various periods of the day, the median was higher for post-lunch period (-35.47 mg/dL IQR: -44.0, -10.22) and lower for post-dinner time (-6.31 mg/dL, IQR: -46.78, 2.05) – Table 4.

Regarding postprandial glucose excursion, there was no statistical difference in this parameter with the use of dapagliflozin. However, at lunch time, there was an improvement in glucose ex-

Table 1. Baseline characteristics of included patients

Age (years), mean (± SD)	36.12 (± 11.06)
[20-29]	7 (41.18%)
[30-39]	4 (23.53%)
[40-49]	4 (23.53%)
[50-59]	1 (5.88%)
[60-69]	1 (5.88%)
Range	22-61
Females, *n* (%)	10 (58.82%)
Duration of type 1 diabetes (years), mean (± SD)	17.65 (±9.50)
Range	3-32
Treatment	
Dapagliflozin 5 mg	7 (41.18%)
Dapagliflozin 10 mg	2 (11.76%)
Dapagliflozin/metformin 5/850 mg	8 (47.06%)
Method of insulin delivery	
CSII, n (%)	11 (64.71%)
MDI, n (%)	6 (35.29%)
Total daily insulin dose (IU/kg/day), mean (± SD)	0.71 (± 0.37)
Body weight (kg), mean (± SD)	88.71 (± 14.82)
BMI (kg/m^2), mean (± SD)	30.79 (±3.11)
eGFR (mL/min/1.73 m^2), mean (± SD)	96.96 (±19.87)
Microvascular complications, n (%)	4 (23.53%)
Diabetic retinopathy	4
Macrovascular complications, n (%)	2 (11.76%)
Stroke	1
Myocardial infarction	1

TSD: standard deviation; CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injection.

Table 2. CGM metrics, body weight and BMI before and after introduction of dapagliflozin.

	Before SGLT2i	After SGLT2i	*p*-value*
TIR (%), mean (± SD)	50.9 (± 13.4)	60.2 (±14.7)	0.019
TIR (minutes), mean (± SD)	710.7 (±178.5)	877.2 (±203.6)	0.006
TAR (%), mean (± SD)	41.5 (±15.2)	32.2 (±15.9)	0.058
TAR (minutes), mean (± SD)	588.8 (±212.6)	460.0 (±227.0)	0.063
TBR (%), median (IQR)	6.0 (2,5-12)	7.0 (4-11)	0.521
TBR (minutes), mean (± SD)	116.9 (±105.9)	103.7 (±55.3)	0.567
CV (%), mean (± SD)	43.7 (±6.2)	40.7 (±6.4)	0.001
GMI (%), median (IQR)	7.6 (7.2-9.2)	7.0 (6.7-7.5)	0.001
Weight (kg), mean (± SD)	88.7 (±14.8)	84.3 (±13.6)	<0.001
BMI (kg/m^2), mean (± SD)	30.8 (±3.1)	29.3 (±2.9)	<0.001

* t-test or Wilcoxon

SD: standard deviation; IQR: interquartil range; TIR: time in range; TAR: time above range; TBR: time below range; CV: coefficient of variation; GMI: glucose management indicator; BMI: body mass index

Table 3. Daily insulin dose and glucose levels before and after introduction of dapagliflozin.

	Before SGLT2i	After SGLT2i	*p*-value*
Fasting glucose (mg/dL), mean (± SD)	169.9 (±30.4)	147.8 (±25.6)	0.028
Pre-meal glucose – lunch (mg/dL), mean (± SD)	178.3 (±36.1)	162.3 (±25.7)	0.028
Pre-meal glucose – dinner (mg/dL), mean (± SD)	173.4 (±55.8)	145.1 (±25.2)	0.025
Post-meal glucose – lunch (mg/dL), mean (± SD)	185.5 (±37.9)	158.4 (±27.8)	0.006
Post-meal glucose – dinner (mg/dL), median (IQR)	195.6 (±34.9)	171.5 (±34.9)	0.078
Postprandial glucose excursion – lunch (mg/dL), mean (± SD)	7.2 (±49.3)	-4.5 (±33.3)	0.290
Postprandial glucose excursion – dinner (mg/dL), mean (± SD)	22.2 (±45.0)	28.9 (±45.9)	0.492
TDD (U), median (IQR)	53.9 (46.5-72.5)	44.0 (40.0-64.9)	0.001
Basal dose (U), median (IQR)	30.0 (26.4-40.0)	25.0 (23.7-33.1)	0.001
Bolus dose (U), median (IQR)	24.7 (19-39.8)	20.0 (15.0-28.3)	0.028

* t-test or Wilcoxon

SD: standard deviation; IQR: interquartil range; TDD: total daily dose

Table 4. Difference between glucose levels after and before dapagliflozin.

Fasting period (median, IQR)	Pre-lunch period (median, IQR)	Post-lunch period (median, IQR)	Pre-dinner period (median, IQR)	Post-dinner period (median, IQR)
-28.77 (-51.48, -12.46)	-20.15 (-35.03, -1.01)	-35.47 (-44.0, -10.22)	-19.12 (-65.11, -1.81)	-6.31 (-46.78, 2.05)

cursion with SGLT2i, with a mean of -4.5 mg/dL (±33.3) versus 7.2 (±49.3) without the drug. Conversely, in what concerns to glucose excursion at dinner time, glucose levels were higher after the introduction of SGLT2i (22.2 ±45.0 mg/dL *vs* 28.9 ±45.9 mg/dL).

Median total daily insulin dose (TDD) reduced significantly from 53.9 U to 44.0 U (p=0.001), as well as basal insulin dose and bolus, which decreased from 30.0 U to 25.0 U (p=0.001) and from 24.7 to 20.0 U (p=0.028), respectively (Table 3).

There was also a statistically significant reduction in weight, with an average value of 4.4 kg (p<0.001) and in BMI, with an average value of 1.51 kg/m^2 (p<0.001) (Table 2).

More than half of the patients (9/17; 52.9%) were taking dapagliflozin alone (7 at the 5 mg dose and 2 at the 10 mg dose) and 8 patients were taking the association with metformin. The independent analysis for patients on monotherapy with dapagliflozin showed a similar trend to that found for the total series, with significant differences in %CV (p=0.012), GMI (p=0.015), post-meal glucose lunch (p=0.019), postprandial glucose excursion – lunch (p=0.008) and weight (p=0.002). Also, the %TIR improved with the introduction of dapagliflozin, although with no statistical difference (58.33% ±14.13 with dapagliflozin *vs* 50.67 % ±16,01, p=0.108). There were no episodes of severe hypoglycemia or ketoacidosis during the study period. Additionally, only 1 patient had a genital infection that did not require treatment interruption.

Discussion

Our study suggests that the introduction of dapagliflozin in T1DM patients led to an overall improvement in glycemic control, with a more pronounced effect on lunch post-prandial glucose levels. Based on the CGM data, time in the target glycemic range, %CV and GMI showed significant improvements. In fact, more than 60% of the CGM readings were in the target range 3 months after the introduction of dapagliflozin, reflecting an additional 2.78 hours of time spent in range every day. These findings are in line with those obtained in DEPICT-2 trial,[7] where 50% of the CGM readings were in target range at week 24. However, no statistical significance was found for %TAR and %TBR, results that are corroborated by the study developed by Suzuki *et al* that aimed to investigate the effects of SGLT2i in glycemic control in a population of Japanese patients with T1DM in a real-world clinical setting.[13] There has been growing evidence that small increments in TIR measured by CGM may have beneficial effects in several diabetes complications,[14,15] thus emphasizing the overall benefits of using SGLT2i in selected patients with type 1 diabetes.

The improvement of %CV found in our study after the introduction of the SGLT2i is described in several other studies, being one of the major advantage of SGLT2 use in T1DM.[16,17] The %CV is correlated with risk of hypoglycemia[18] and, since the glucose-lowering effect of SGLT2i is insulin independent and glucose dependent, it is accompanied by reduced glucose variability.[2]

The GMI is the accepted method for using CGM-derived mean glucose to estimate lab-tested HbA1c. In the DEPICT 1 and 2 studies, the improvement in HbA1c with dapagliflozin was seen from week 4 of treatment and maintained to week 24. In a pooled analysis of the DEPICT studies, 39% and 11% of dapagliflozin 5 mg/day and placebo recipients achieved an HbA1c reduction of ≥ 0.5% without weight gain at week 24.[6,7] The significant reduction of GMI observed in this population (from 7.6% to 7%) reflects the positive effect of dapagliflozin in glycemic control, namely in the reduction of mean glucose levels.

Regarding glycemic excursion, although with no statistical significance, the introduction of dapagliflozin showed favorable results at lunch period, with levels that ranged from 7.2 mg/dL (±49.3) without SGLT2i to -4.5 mg/dL (±33.3), reflecting a mean lower glucose value after this meal with dapagliflozin.

Additionally, this study revealed a more pronounced effect of dapagliflozin at lunch time. In fact, when assessing glucose concentrations at pre- and post-lunch periods with and without dapagliflozin, a significant statistical difference was found. Furthermore, although with no statistical difference, glucose excursion was lower in this period with the SGLT2i in therapeutic regimen. On the contrary, at dinner time, glucose excursion with dapagliflozin did not improve and a statistical difference in glucose concentrations was only identified at pre-dinner time. Moreover, considering the difference between glucose levels after and before the introduction of dapagliflozin as a variable, the median was higher at post-lunch period (-35.45 mg/dL). The lowest median was observed at post-dinner period (-6.31 mg/dL). We do not have a definite explanation to the latter findings, but there are several possible explanations. All the patients included in this study took dapagliflozin after breakfast. As maximum plasma concentrations (C max) of this drug are usually achieved within 2 hours after administration in the fasted state,[19] this may have contributed to the better results obtained at lunch period due to better anti-hyperglycemic effect at lunch time. Furthermore, dapagliflozin and other SGLT2i have also been associated with increase in caloric intake, with some degree of carbohydrate craving, due to central nervous system activation, mainly in the left putamen. The higher plasmatic concentration at lunch time may also be associated with a higher intake of carbohydrates at lunch. A simpler explanation may be the intake of more carbohydrates or carbohydrates with a higher glycemic index at lunch time in comparison with dinner, leading to a more pronounced effect of dapagliflozin in the mitiga-

tion of glucose excursion at lunch time.[20,21]

The significant reduction of weight and BMI obtained in this population is recognized as one of the most beneficial reported effects in literature.[22] There was a mean reduction of 4.4 kg during follow-up, in a population whose baseline BMI was 30.79 kg/m2. Indeed, this drug has received approval for T1DM patients with BMI >27 kg/m^2. This BMI restriction reflects safety concerns around DKA risk in those with a lower BMI.[15,23] This weight reduction was similar in several other studies with either dapagliflozin or other SGLT2i.[3] The consistent reduction of body weight observed with dapagliflozin might also be important for some patients to limit later cardiovascular risk.[3]

In addition to body weight, several other clinical criteria have been pointed out as crucial to introduce this drug class in T1DM. Patients that require insulin dose injection of at least 0.5 units/kg of body weight per day were identified as candidates who mostly benefit from this therapeutic approach.[24] Our study population had a mean of total insulin dose per day of 0.71 units/kg of body weight per day, which is in accordance with the recommendations.

Other relevant finding was the significant reduction of TDD, basal dose and bolus dose after the introduction of dapagliflozin. These results were found in several other studies and may explain why the use of dapagliflozin as an adjuvant treatment allow better glycemic control without increasing the risk of hypoglycemia.[25] It may also contribute to the weight reduction observed after the introduction of the SGLT2 inhibitor.

In our study, eight patients were taking metformin in association with dapagliflozin. In the recent ADA-EASD consensus on the management of type 1 diabetes, the role of adjuvant therapies was comprehensively reviewed. Metformin is considered to have a minimal effect in glycaemia reduction (≈ 0,1% reduction in HbA1c) and a modest effect in weight, with no impact in insulin doses.[26] Considering the latter findings, we think that the overall glycemic benefit was due to dapagliflozin, despite a concomitant small effect of metformin may also have contributed to the final results.

One important aspect related with the use of SGLT2i in T1DM is tolerability and safety. Actually, the use of this drug class has potential associated adverse effects. Diabetic ketoacidosis (DKA) is an important complication of type 1 diabetes, and the risk is increased when SGLT inhibitors are used in this population. Furthermore, patients and healthcare providers must be aware that DKA associated with the use of these drugs may have an atypical presentation, as the glucose levels may be inappropriately normal – euglycemic DKA.[3] Therefore, it is recommended that the patients take part of an education program for DKA, including aspects like monitoring ketones, when to seek for medical help, when to stop the medication, and the need to avoid alcohol, illicit drugs or restrictive diets (low carbohydrate restriction or ketogenic diet).[17,27] The prevalence of DKA in the DEPICT and inTandem1 and inTandem2 studies ranged from 2% to 3% at week 24, being higher with higher doses of SGLT2i.[6,7,9] In our study, there were no episodes of DKA, probably because of the short time of follow-up and because the patients were strictly selected. Actually, T1DM patients that start SGLT2i in our center must be able to monitor blood glucose and capillary blood ketones regularly, and are educated on how to monitor rising levels of each, in addition to recognizing DKA. Also, the poorly compliant with insulin therapy and those who had episodes of DKA in previous month are not eligible. Equally, patients are advised to withdrawn SGLT2i during intercurrent illness, and increase frequency of glucose and ketone monitoring.

SGLT2i are also associated with an increased risk of genital mycotic infections, notably in premenopausal women. The increased risk of genital mycotic infections associated with SGLT2i has also been reported in a real-world setting study.[28] Although these infections have the potential to impact quality of life, the majority can be easily managed and do not necessitate dapagliflozin discontinuation. In our sample, only one female patient (5.88%) had a genital infection during the study period that was solved without the need to interrupt medication. This percentage is lower than the reported in literature (12% in DEPICT-1 study), probably because of the shorter follow-up.[6]

The withdrawn of type 1 diabetes indication for dapagliflozin by the pharmaceutical company has been a surprise. The company has argued that required changes to the product label would cause confusion among doctors when prescribing it for other conditions. However, UK and UE medicines regulators only advised that despite there being no new safety or efficacy concern, an inverted black triangle would need to be added to the label to signify the need of additional monitoring.[29]

The present study has some limitations. First, this was a single-arm retrospective and observational study, with no control group. Second, the number of patients included was small and the follow-up time was short, so the long-term effects could not be assessed. Also, other important factors, as the physical activity were not considered. Prospective studies evaluating long-term effects and safety of SGLT2 inhibitors in patients with type 1 diabetes are warranted.

Conclusion

The introduction of SGLT2i in this population improved glycemic control during the pre and postprandial periods. The maximal effect was observed in post-lunch period, possibly because of the therapeutic prescription schedule.

This reinforces the evidence that dapagliflozin could play a relevant role in the management of selected patients with T1DM, helping to address several important unmet treatment needs, including improved glycemic control with decreased glycemic variability, weight loss, and decrease in insulin dose.

Contributorship Statement / Declaração de Contribuição:

MAL: study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation.
BA: data collection, analysis and interpretation of results.
MM and LB: study conception and design, supervision.
IP: supervision.

All authors reviewed the results and approved the final version of the manuscript.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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References / Referências

1. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. Clin Diabetes. 2008;26:77-82.
2. Petrie JR. SGLT2 inhibitors and renal complications in type 1 diabetes. Lancet Diabetes Endocrinol. 2020;8:803-5. doi: 10.1016/S2213-8587(20)30311-9.
3. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium–glucose cotransporter (SGLT) Inhibitors. Diabetes Care. 2019;42:1147-54. doi: 10.2337/dc18-2316.
4. Song P, Onishi A, Koepsell H, Vallon V. Sodium glucose cotransporter SGLT1 as a therapeutic target in diabetes mellitus. Expert Opin Ther Targets. 2016;20:1109-25. doi: 10.1517/14728222.2016.1168808.
5. Taylor SI, Blau JE, Rother KI, Beitelshees AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. Lancet Diabetes Endocrinol. 2019;7:949-58. doi: 10.1016/S2213-8587(19)30154-8.
6. Dandona P, Mathieu C, Phillip M, Hansen L, Griffen SC, Tschope D, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5:864-76.
7. Mathieu C, Dandona P, Gillard P, Senior P, Hasslacher C, Araki E, et al. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial. Diabetes Care. 2018;41:1938-46.
8. Dandona P, Mathieu C, Phillip M, Hansen L, Tschope D, Thoren F, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-Week Study. Diabetes Care. 2018;41:2552-9. doi: 10.2337/dc18-1087.
9. Buse JB, Garg SK, Rosenstock J, Bailey TS, Banks P, Bode BW, et al. Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. Diabetes Care. 2018;41:1970-80. doi: 10.2337/dc18-0343.
10. Danne T, Cariou B, Banks P, Brandle M, Brath H, Franek E, et al. HbA1c and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. Diabetes Care. 2018;41:1981-90. doi: 10.2337/dc18-0342.
11. Rosenstock J, Marquard J, Laffel LM, Neubacher D, Kaspers S, Cherney DZ, et al. Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials. Diabetes Care. 2018;41:2560-9. doi: 10.2337/dc18-1749.
12. Forxiga (dapagliflozin) 5mg should no longer be used for the treatment of Type 1 Diabetes Mellitus 2021 [accessed 2022-05-17]. Available from: https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-forxiga-dapagliflozin-5mg-should-no-longer-be-used_en.pdf .
13. Suzuki D, Yamada H, Yoshida M, Funazaki S, Amamoto M, Morimoto J, et al. Sodium-glucose cotransporter 2 inhibitors improved time-in-range without increasing hypoglycemia in Japanese patients with type 1 diabetes: A retrospective, single-center, pilot study. J Diabetes Investig. 2020;11:1230-7. doi: 10.1111/jdi.13240.
14. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42:1593-603. doi: 10.2337/dci19-0028.
15. Evans M, Hicks D, Patel D, Patel V, McEwan P, Dashora U. Optimising the Benefits of SGLT2 Inhibitors for Type 1 Diabetes. Diabetes Ther. 2020;11:37-52. doi: 10.1007/s13300-019-00728-6.
16. Paik J, Blair HA. Dapagliflozin: A Review in Type 1 Diabetes. Drugs. 2019;79:1877-84. doi: 10.1007/s40265-019-01213-x.
17. Garg SK, Peters AL, Buse JB, Danne T. Strategy for Mitigating DKA Risk in Patients with Type 1 Diabetes on Adjunctive Treatment with SGLT Inhibitors: A STICH Protocol. Diabetes Technol Ther. 2018;20:571-5. doi: 10.1089/dia.2018.0246.
18. Rodbard D. Glucose Variability: A Review of Clinical Applications and Research Developments. Diabetes Technol Ther. 2018;20:S25-S215. doi: 10.1089/dia.2018.0092.
19. Forxiga - Summary of Product Characteristics [accessed 22-02-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf .
20. Ferrannini E. Sodium-Glucose Co-transporters and Their Inhibition: Clinical Physiology. Cell Metab. 2017;26:27-38. doi: 10.1016/j.cmet.2017.04.011.
21. van Ruiten CC, Veltman DJ, Schrantee A, van Bloemendaal L, Barkhof F, Kramer MH, et al. Effects of Dapagliflozin and Combination Therapy With Exenatide on Food-Cue Induced Brain Activation in Patients With Type 2 Diabetes. J Clin Endocrinol Metab. 2022;107:e2590-9. doi: 10.1210/clinem/dgac043.
22. Riddle MC, Cefalu WT. SGLT inhibitors for type 1 diabetes: an obvious choice or too good to be true? Diabetes Care. 2018;41:2444-7. doi: 10.2337/dci18-0041.
23. Mathieu C, Dandona P, Birkenfeld AL, Hansen TK, Iqbal N, Xu J, et al. Benefit/risk profile of dapagliflozin 5 mg in the DEPICT-1 and -2 trials in individuals with type 1 diabetes and body mass index >/=27 kg/m(2). Diabetes Obes Metab. 2020;22:2151-60. doi: 10.1111/dom.14144.
24. Erskine D. Dapagliflozin for type 1 diabetes: ensuring benefits outweigh the risks. Drug Ther Bull. 2020;58:34. doi: 10.1136/dtb.2019.000081.
25. Mathieu C, Dandona P, Phillip M, Oron T, Lind M, Hansen L, et al. Glucose Variables in Type 1 Diabetes Studies With Dapagliflozin: Pooled Analysis of Continuous Glucose Monitoring Data From DEPICT-1 and -2. Diabetes Care. 2019;42:1081-7. doi: 10.2337/dc18-1983.
26. Holt RI, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2021;44:2589-625. doi: 10.1007/s00125-021-05568-3.
27. Goldenberg RM, Gilbert JD, Hramiak IM, Woo VC, Zinman B. Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: The STOP DKA Protocol. Diabetes Obes Metab. 2019;21:2192-202. doi: 10.1111/dom.13811.
28. Lega IC, Bronskill SE, Campitelli MA, Guan J, Stall NM, Lam K, et al. Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: A population-based study of older women and men with diabetes. Diabetes Obes Metab. 2019;21:2394-404. doi: 10.1111/dom.13820.
29. Mahase E. Type 1 diabetes drug was withdrawn because of a “commercial conflict of interest,” charity argues. BMJ.2022;376:o373 doi: 10.1136/bmj.o373.

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Artigo Original

Lower Prevalence of Subclinical Hypothyroidism in Vegetarian Men Compared with Omnivores

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A B S T R A C T

Introduction: Subclinical hypothyroidism (SCH) is diagnosed when the TSH level is elevated above the reference range (0.4-4.5 µUl/mL) and free T4 levels remain within the normal serum range (0.7-1.7 ng/dL). There are many studies showing that a vegetarian dietary pattern could bring benefits at multiple levels. The objective of this study was to investigate the association between dietary pattern and thyroid hormones, as well as to compare the prevalence of SCH among apparently healthy vegetarian (VEG) and omnivorous (OMN) male individuals.
Methods: The study was based on data from two 24-hour dietary recalls, biochemical parameters, and anthropometry obtained from 88 individuals VEG (n = 44) and OMN (n = 44) male, between 35 and 71 years of age, who were participants in the CARVOS study.
Results: The VEG group was found to have TSH values significantly lower than the values found in the OMN group ($p = 0.049$). The prevalence of SCH was 6 times higher in the OMN group when compared to the VEG values (13% OMN versus 2.3% VEG, $p = 0.039$), it was confirmed by multiple logistic regression, in which the OMN group was more likely to have SCH.
Conclusion: The VEG group obtained significantly lower TSH values and were significantly less likely to have SCH compared with those who follow a OMN dietary pattern.

Menor Prevalência de Hipotiroidismo Subclínico em Homens Vegetarianos Comparados aos Onívoros

R E S U M O

Introdução: O hipotiroidismo subclínico (HSC) é diagnosticado quando o nível de TSH está elevado acima da faixa de referência (0,4-4,5 µUl/mL) e os níveis de T4 livre permanecem dentro da faixa sérica normal (0,7-1,7 ng/dL). Muitos estudos mostram que um padrão alimentar vegetariano pode trazer benefícios em vários níveis. O objetivo deste estudo foi investigar a associação entre o padrão alimentar e as hormonas tiroideias, bem como comparar a prevalência de HSC em indivíduos aparentemente saudáveis vegetarianos (VEG) e omnívoros (OMN) do sexo masculino.
Metodologia: O estudo baseou-se em dados de dois registos alimentares de 24 horas, parâmetros bioquímicos e antropometria, obtidos de 88 indivíduos VEG (n = 44) e OMN (n = 44) do sexo masculino, entre 35 e 71 anos, entre os participantes do estudo CARVOS.

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Resultados: O grupo VEG apresentou valores de TSH significativamente menores do que os valores encontrados no grupo OMN (p = 0,049). A prevalência de HSC foi 6 vezes maior no grupo OMN quando comparada aos valores de VEG (13% OMN *versus* 2,3% VEG, p = 0,039), confirmada por regressão logística múltipla, na qual o grupo OMN era mais provável a ter HSC.
Conclusão: O grupo VEG apresentou menores valores de TSH e foram significativamente menos propensos a terem HSC em comparação aos indivíduos do grupo OMN.

Introduction

Hypothyroidism is present when the levels of the thyroid hormone thyroxine (T4) and triiodothyronine (T3) are below the reference range, indicating thyroid failure. Due to thyroid dysfunction, the levels of thyrotropin or also called thyroid stimulating hormone (TSH) are elevated, being an important clinical expression. Subclinical hypothyroidism (SCH) is diagnosed when the TSH level is elevated above the reference range (0.4-4.5 µUl/mL) and free T4 levels remain within the normal serum range (0.7-1.7 ng/dL).[1,2] There is a lack of evidence regarding the risk factors associated with SCH. It is important to review its epidemiology, with recommendations for appropriate evaluation, exploring the risks and benefits of treatment and the consequences of nontreatment.[3]

The normal function of the thyroid gland depends on the presence of trace elements for the metabolism and synthesis of thyroid hormones.[4,5] Nutrient deficiency can affect the endocrine system, leading to several disorders, such as hypothyroidism.6 In this sense, knowledge of the influence of dietary patterns on SCH is of paramount importance.

There are many studies showing that a vegetarian dietary pattern could bring benefits at multiple levels, such as physiology,[7] microbiology,[8] biomarkers[9] and genetics.[10] Thus, we hypothesized that there could be a difference in the prevalence of SCH among individuals with different dietary patterns.

The objective of this study was to investigate the association between dietary pattern and thyroid hormones, as well as to compare the prevalence of SCH among apparently healthy vegetarian and omnivorous male individuals.

Methods

A sample of 88 male subjects, between 35 and 71 years of age, was selected from the participants in the CARVOS study (Carotid Atherosclerosis and Arterial Stiffness of Vegetarian and Omnivorous Individuals). The inclusion and exclusion criteria have been previously described.[7]

A 24-hour food recall for two days a week was applied to characterize dietary patterns. Those who did not consume any type of meat (all animals included) for at least four years (n = 44) were classified as vegetarian (VEG), and those who consumed meat regularly at least four times a week (n = 44) were classified as omnivorous (OMN).

Blood samples were collected after the patient fasted for 10 to 12 hours. Serum lipids, including triglycerides (TG), total cholesterol (TC) and high-density lipoprotein (HDL-c), were analyzed using enzymatic methods with an automatic multichannel chemical analyzer (Siemens Healthcare, Newark, NJ, USA) at the InCor Central Laboratory. Low-density lipoprotein cholesterol (LDL-c) was calculated using Friedenwald's formula for TG levels < 400 mg/dL. As for TSH, T3, T4, and free T4 were analyzed by competitive immunoassay methods using direct chemiluminescent technology. The quality control assessment was carried out daily for all determinations.

Subclinical hypothyroidism was diagnosed when the TSH level is elevated above the reference range (0.4-4.5 µUl/mL) and free T4 levels remain within the normal serum range (0.7-1.7 ng/L).[1,2]

A database for Brazilian food composition was used to calculate the daily intake of energy and nutrients.[11] The iodine intakes were estimated from the total sodium calculated in the diet. For this, the salt iodization values recommended by federal legislation were used as the basis[12,13] and recommendations were used from the Dietary Reference Intakes (DRI) for consumption of iodine and more nutrients for adults.[14] Referred food supplements were recorded for frequency of use and dosage and calculated along with the diet.

The data are presented as mean ± standard deviation (SD), and categorical variables are shown as percentage and number (n). The unpaired Student t test and the Chi-square test were used to test differences for numerical and nominal variables.

To test the association between the dietary pattern (VEG and OMN) and SCH, a multiple logistic regression was performed, considering body mass index (BMI) adjustment variables and daily iodine consumption.

All analyzes were performed using Stata (10.0) (StataCorp, LLC, College Station, TX).

Results

Table 1 shows the average age, BMI, and waist/hip ratio of the study participants. The average duration of vegetarianism was 17.8 ± 12.5 years. Age was similar between groups; however,

Table 1. Anthropometric characteristics, biochemical parameters, average consumption of calories and nutrient intake of vegetarians and omnivores.

Variables	VEG (n=44)	OMN (n=44)	p
Age	45.5 ± 7.8	46.8 ± 9.6	0.23
BMI (kg/m²)	23.1 ± 2.9	27.2 ± 4.8	<0.001
Waist/hip ratio	0.87 ± 0.1	0.92 ± 0.1	<0.001
DBP	75.2 ± 8.6	83.9 ± 10.4	<0.001
SBP	119.5 ± 10.4	129.2 ± 15.1	<0.001
TC (mg/dL)	180.1 ± 40.5	202.7 ± 35.3	0.003
HDL-c (mg/dL)	47.6 ± 9.3	45.5 ± 11.6	0.17
LDL-c (mg/dL)	110 ± 33.2	128.5 ± 32.4	0.005
Non-HDL-c (mg/dL)	132.5 ± 43.2	157.3 ± 36.6	0.002
Triglycerides (mg/dL)	112.2 ± 72.2	143.9 ± 64	0.016
TSH (µUI/mL)	2.2 ± 1.1	2.7 ± 1.8	0.049
T3 (ng/mL)	1.2 ± 1.1	1.2 ± 1.2	0.262
T4 (µg/dL)	8.3 ± 7.9	8.2 ± 7.7	0.302
Free T4 (ng/dL)	1.1 ± 1.0	1.1 ± 1.1	0.420
Calories (kcal)	2177 ± 559	2348 ± 736	0.11
Protein (% of energy)	17.1 ± 7.8	19.5 ± 4.5	0.04
Carbohydrate (% of energy)	63.2 ± 11.6	51.9 ± 9.7	<0.001
Lipids (% of energy)	24.8 ± 8.3	29.1 ± 7.2	0.006
Sodium (mg)	2334.1 ± 1665.3	2633.6 ± 1452.6	0.185
Iodine (mcg)	175.1 ± 124.9	197.5 ± 108.9	0.371
Zinc (mg)	9.0 ± 3.2	12.7 ± 5.8	<0.001
Iron (mg)	21.9 ± 14.6	17.05 ± 5.5	0.042

Data are given as median + standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; Non-HDL-c, non-high-density lipoprotein. TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

BMI and waist/hip ratio, systolic blood pressure and diastolic blood pressure were significantly lower in VEG compared with OMN individuals.

The consumption of zinc was higher in omnivorous individuals ($p < 0.001$) and the consumption of iron was higher in vegetarians ($p = 0.042$).

VEG group was found to have TSH values significantly lower than the values found in the OMN group ($p = 0.049$).

The prevalence of SCH was 6 times higher in the OMN group when compared to the VEG values (13% OMN *vs* 2.3% VEG), a significant difference ($p = 0.039$).

In addition, according to multiple logistic regression in relation to SCH, adjusted for age, BMI, and daily iodine consumption, the OMN group was significantly more likely to have SCH (OR: 13.59, 95% CI 1.20–153.44).

Discussion

As described in this work, it is possible to demonstrate differences regarding the prevalence of SCH among apparently healthy VEG male individuals compared with OMN individuals. To the best of our knowledge, this is the first Latin American study to compare VEG and OMN dietary patterns and their possible relationship with the development of SCH.

Although the mean TSH values of VEG and OMN of our samples are within the reference values, it is noted that the OMN group has significantly higher values compared to the VEG group. The values of T3, T4, and free T4 were not significantly different between groups.

The OMN group was significantly more likely to have SCH, when adjusted for age, BMI, and estimated iodine consumption. Studies of descriptive characteristics carried out by Tostad *et al*,[6] comparing prevalent cases, incidental cases, and cases without hypothyroidism, obtained data demonstrating the strict vegetarian dietary pattern was associated with protection against hypothyroidism, even though the lack of iodine is a risk associated with the complete exclusion of products of animal origin.

Regarding dietary pattern, the OMN group had a higher consumption of protein intake, total fat, saturated fat, and cholesterol, and a lower intake of carbohydrates, mono- and polyunsaturated fat, fiber, potassium, and magnesium ($p < 0.05$) described in the CARVOS study.[7] Possibly, the significantly higher TSH values of the OMN group are influenced by the observed food pattern, typical of the West. Thus, following a vegetarian food pattern could act as protection from thyroid dysfunction.

The vegetarian dietary pattern is shown to be a protective factor in relation to cardiovascular outcomes.[7] In addition, SCH can play a mediating role in this process. In the present study, the VEG group had a lower prevalence of SCH and lower values of TC, LDL-c, non-HDL-c, and triglycerides.

A meta-analysis that analyzed 16 articles suggested that there were higher serum TC, LDL-c, and triglycerides levels in patients with SCH compared with participants with euthyroidism (EU).[15]

Restrictive and/or unbalanced diets can lead to a deficiency of certain minerals, which in turn can contribute to a decrease in the production of thyroid hormones.[16] Unfortunately, selenium values are not presented in this study, because the Brazilian food composition databases do not analyze this nutrient, making it impossible to quantify it based on the individual´s dietary pattern.

In the present study, iron consumption was higher in the VEG group ($p = 0.042$). Much is speculated about the levels of iron in vegetarians, and similar findings are found in the literature regarding the higher consumption of iron in vegetarians.[17,18] According to Zimmermann and Köhrle,[19] the activity of thyroid peroxidase is reduced in iron deficiency. This enzyme present in thyroid cells acts in the synthesis of thyroid hormones. Increased iron consumption could be protective for SCH. Regarding the zinc consumption was higher in the OMN group ($p < 0.001$), as already observed in the literature[20] due to the greater presence of this nutrient in meat and the presence of phytates in plant foods, reducing its absorption.[21] Studies have shown that zinc deficiency adversely affects the synthesis, metabolism, and action of thyroid hormones.[22] Consumption of both nutrients was within the DRI recommendation,[14] according to 24-hour recall calculation. It was not possible to verify these nutrients in serum test in the blood and further studies are needed to explain these points.

Both nutrients were not serum verified, only estimated through the diet, and consumed by groups as recommended by the DRI according to 24-hour recall calculation.

In our study, the estimated value of iodine and sodium consumption was similar in both groups, being above the recommended daily allowance value (150 mcg/day and 1500 mg/day).[14]

Serum TSH levels are known to be positively associated with body weight.[23] Slightly elevated serum TSH levels already demonstrate an increased prevalence of obesity.[24] It is believed that the increase in body mass causes an increase in serum TSH, and not the other way around.[25] The values of BMI and waist/hip ratio were significantly higher in the OMN group, a result that has already been discussed in a previous study.[26]

Other factors can influence a deregulation of the thyroid gland, such as age. Aging is an important factor and is associated with an increased risk of SCH diagnosis. It is known that the prevalence of SCH increases with age.[27] As seen in the present study, the average age of both groups was 46.1 years.

As limitations of the present study, its cross-sectional design, which does not allow testing of causal relationships, should be considered. It was also not possible to calculate iodine and selenium in the recalls used, due to the absence of these minerals in the Brazilian food composition databases. Because of this, iodine intake was estimated from iodized salt. It is unknown the state of autoimmunity status (thyroid autoantibodies) of the original sample, as well as the presence of a family history of thyroid pathology or a personal or family history of autoimmune diseases.

As strengths of the study, it should be noted that the sample, although small, is strongly homogenized, with same-sex and apparently healthy individuals. Additionally, this is a topic little explored by the scientific community, and the findings of the present study may represent yet another factor in protecting the vegetarian dietary pattern. In addition, there are no studies on this theme comparing Latin American VEG and OMN individuals.

Conclusion

In our study, the VEG group obtained significantly lower TSH values compared with the OMN group. Furthermore, multiple logistic regression, adjusted for age, BMI, and estimated daily iodine consumption suggests that adult male individuals who follow an OMN diet, typical of Western countries, are significantly more likely to have SCH compared with those who follow a VEG food standard. Further studies should be carried out comparing these two groups, with the aim of consolidating the relationship between the different dietary patterns and the occurrence of SCH.

Contributorship Statement / Declaração de Contribuição:

JAN and LA: study conception and design, data collection, analysis and draft manuscript preparation.
LFD, EPF, MCPFO and PAC: were responsible for interpretation of results, writing and review.
All authors: reviewed and approved the final version of the manuscript.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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References / Referências

1. Biondi B, Cooper DS. Thyroid hormone therapy for hypothyroidism. Endocrine. 2019;66:18-26. doi: 10.1007/s12020-019-02023-7.
2. Rizzo LFL, Mana DL. Treatment of hypothyroidism in special situations. Medicina. 2020;80 Suppl 6:83-93.
3. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228-38. doi: 10.1001/jama.291.2.228.
4. Hanif S, Ilyas A, Shah MH. Statistical evaluation of trace metals, TSH and T4 in blood serum of thyroid disease patients in comparison with controls. Biol Trace Elem Res. 2018;183:58-70. doi: 10.1007/s12011-017-1137-5.
5. Liu Y, Liu S, Mao J, Piao S, Qin J, Peng S, et al. Serum trace elements profile in graves' disease Environ Sci Pollut Res patients with or without orbitopathy in Northeast China. Biomed Res Int. 2018;2018:3029379. doi: 10.1155/2018/3029379.
6. Tonstad S, Nathan E, Oda K, Fraser GE. Vegan diets and hypothyroidism. Nutrients. 2013:5:4642-52.
7. Acosta-Navarro JC, Antoniazzi L, Oki AM, Bonfim MC, Hong V, Acosta-Cardenas P, et al.? Reduced subclinical carotid vascular disease and arterial stiffness in vegetarian men: The CARVOS Study. Int J Cardiol. 2017;230:562–6.
8. Tomova A, Bukovsky I, Rembert E, Yonas W, Alwarith J, Barnard ND, et al. The effects of vegetarian and vegan diets on gut microbiota. Front Nutr. 2019;6:47. doi: 10.3389/fnut.2019.00047.
9. Acosta-Navarro JC, Gouveia LA, Rocha-Penha L, Cinegaglia N, Belo V, Castro MM, et al. Reduced levels of potential circulating biomarkers of cardiovascular diseases in apparently healthy vegetarian men. Clin Chim Acta. 2016;461:110-3. doi: 10.1016/j.cca.2016.08.002.
10. Krajcovicová-Kudlácková M, Valachovicová M, Pauková V, Dusinská M. Effects of diet and age on oxidative damage products in healthy subjects. Physiol Res. 2008;57:647–51. doi: 10.33549/physiolres.931244.
11. Anção MS, Cuppari L, Tudisco ES, Draibe SA, Sigulem DM. NutWin: Programa de Apoio à Nutrição [Computer Software]. Versão 2.5. Centro de Informática em Saúde, Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, 2002. [Accessed March 7, 2021]. Available at: https://scholar.google.com.br/citations?user=mpuFecMAAAAJ&hl=pt-BR.
12. Agência Nacional de Vigilância Sanitária – ANVISA. Programa Nacional para Prevenção e Controle dos Distúrbios por Deficiência de Iodo [internet]. Brasilia: DF; c2020 [Accessed March 7, 2021]. Available at: http://antigo.anvisa.gov.br/programas-de-monitoramento.
13. Ministério da Saúde, Brasil (BR). RESOLUÇÃO DA - RDC Nº 23, DE 24 DE ABRIL DE 2013. Dispõe sobre o teor de iodo no sal destinado ao consumo humano e dá outras providências. [Internet] Diário Oficial União. 24 abril 2013; Seção 1. [Accessed March 7, 2021]. Available at: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2013/res0023_23_04_2013.html.
14. PadovaniI RM, Amaya-Farfán J, Colugnati FAB, Domene SMA.? Dietary reference intakes: application of tables in nutritional studies. Rev Nutrição. 2006;19:741-60.
15. Liu X, He S, Zhang SF, Wang J, Sun XF, Gong CM, et al. Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. Med Sci Monit. 2014;20:1432-41. doi: 10.12659/MSM.891163.
16. Mezzomo TR, Nadal J. Effect of nutrients and dietary substances on thyroid function and hypothyroidism. DEMETRA. 2016;11:427-43.
17. Bedford JL, Barr SI. Diets and selected lifestyle practices of self-defined adult vegetarians from a population-based sample suggest they are more 'health conscious'. Int J Behav Nutr Phys Act. 2005;2:4.
18. Farmer B. Nutritional adequacy of plant-based diets for weight management: observations from the NHANES. Am J Clin Nutr. 2014;100:365-8. doi: 10.3945/ajcn.113.071308.
19. Zimmermann MB, Köhrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid. 2002;12:867-78. doi: 10.1089/105072502761016494.
20. Foster M, Chu A, Petocz P, Samman S. Effect of vegetarian diets on zinc status: a systematic review and meta-analysis of studies in humans. J Sci Food Agric. 2013;93:2362-71. doi: 10.1002/jsfa.6179.
21. Foster M, Samman S. Vegetarian diets across the lifecycle: impact on zinc intake and status. Adv Food Nutr Res. 2015;74:93-131. doi: 10.1016/bs.afnr.2014.11.003.
22. O'Kane SM, Mulhern MS, Pourshahidi LK, Strain JJ, Yeates AJ. Micronutrients, iodine status and concentrations of thyroid hormones: a systematic review. Nutr Rev. 2018;76:418-31. doi: 10.1093/nutrit/nuy008.
23. Asvold BO, Bjøro T, Vatten LJ. Association of serum TSH with high body mass differs between smokers and never-smokers. J Clin Endocrinol Metabol. 2009;94:5023-27. doi: 10.1210/jc.2009-1180.
24. Monzani F, Caraccio N, Kozàkowà M, Dardano A, Vittone F, Virdis A, et al. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo controlled study. J Clin Endocrinol Metabol. 2004;89:2099-106. doi: 10.1210/jc.2003-031669.
25. Lips MA, Pijl H, van Klinken JB, de Groot GH, Janssen IM, Van Ramshorst B, et al. Roux-en-Y gastric bypass and calorie restriction induce comparable time-dependent effects on thyroid hormone function tests in obese female subjects. Eur J Endocrinol. 2013 Aug 28;169(3):339-47. doi: 10.1530/EJE-13-0339.
26. Acosta-Navarro JC, Antoniazzi L, Oki AM, Bonfim MC, Hong V, Bortolotto LA, et al. Prevalence of metabolic syndrome and Framingham Risk Score in apparently healthy vegetarian and omnivorous men. Arq Brasil Cardiol. 2018;110:430-7.
27. Leng O, Razvi S. Hypothyroidism in the older population. Thyroid Res. 2019;12:2. doi: 10.1186/s13044-019-0063-3.

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Artigo Revisão

Type 1 Diabetes and Exercise Management among Children and Adolescents: An Overview

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A B S T R A C T

Exercise is determinant to the management of type 1 diabetes mellitus. Despite being crucial for a healthy development, it brings several challenges for patients, families and professionals that deal with insulin therapy. In fact, the type, duration, intensity of the exercise (among several other factors) can have an important impact on glycemic control. For that reason, this paper aims to present an overview of some basic concepts related with exercise in children and adolescents with type 1 diabetic patients, that will be useful for clinicians to develop an effective management that enables this activity while avoiding hypo and hyperglycemia.

Diabetes Tipo 1 e Gestão da Prática de Exercício Físico em Idade Pediátrica

R E S U M O

O exercício é determinante para a abordagem terapêutica da diabetes *mellitus* tipo 1. Apesar de ser crucial para um desenvolvimento saudável, a sua prática dá origem a diversos desafios para doentes, familiares e profissionais que lidam com a terapêutica insulínica. De facto, o tipo, duração, intensidade do exercício (entre vários outros fatores) podem ter um impacto importante no controlo glicémico. Por esse motivo, este artigo tem como objetivo apresentar uma visão geral de alguns conceitos básicos relativos ao exercício em doentes com diabetes tipo 1, que serão úteis para que os clínicos desenvolvam uma gestão terapêutica eficaz que possibilite esta atividade, evitando hipo e hiperglicemias.

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Introduction

The management of type 1 diabetes mellitus (T1D) settles in three main pillars: (1) insulin, (2) proper nutritional guidance and (3) regular exercise. This activity presents several benefits among children and adolescents: improves body composition, cardiorespiratory fitness, blood lipid profile and psychological well-being while decreases total daily insulin needs, episodes of severe hypo- or hyperglycemia and end-organ damage. The relevance of this therapeutical pillar becomes even clearer when considering that many T1D patients are overweight/ obese and that cardiovascular disease remains the leading cause of mortality and morbidity among young T1D patients.[1-4] Therefore, it is unsurprising that all T1D pediatric patients with 6 years or more are advised to engage in at least 60 minutes of physical exercise daily, similarly to healthy children. This should encompass moderate to vigorous aerobic activities most of the time, but also musculoskeletal strengthening exercises.[4]

Although exercise is essential for a healthy development, it poses several challenges for families and professionals that manage insulin therapy in T1D patients.[5] For instance, planned adjustments of carbohydrates or insulin are challenging in young children because physical activity is frequently based around play, which is usually unplanned and variable from day to day. Conversely, older children and adolescents usually engage in more structured exercise (school sports, or other extracurricular activities, such as competitive ones), where exercise strategies to prevent hypo- or hypoglycemia are more easily applied.[6] In addition, growth and pubertal development influence glucose levels,[7] adding to a myriad of factors that also impact glycemic response to exercise (including type, duration of the exercise, intensity, amount of active insulin, anxious behavior, among others).[6]

Thus, this paper aims to summarize the physiological mechanisms and basic practical concepts surrounding exercise in pediatric T1D patients, providing the necessary tools to the clinician for the development of an effective diabetes management plan.

The physiology of exercise in type 1 diabetes and its clinical consequences

The key for a successful therapeutic management strategy lies on a thorough knowledge of the exercise physiology. Exercise can be classified into three main groups: aerobic, anaerobic or combined exercises. Aerobic activities comprise repeated sequences of light to vigorous intensity exercise for extended periods (at least 10 minutes), involving large muscle groups and being usually associated with blood glucose reductions in T1D patients. In contrast, anaerobic activities are typically very high intensity efforts lasting for a short time (seconds to minutes). These activities are fueled by energy sources located within the muscles that are independent of the use of inhaled oxygen, being frequently associated with elevations in blood glucose.[8,9] Combined exercises encompass repeated bouts of intense activities interspersed with low to moderate intensity or rest; these include multiple common playground activities, such as soccer or other team sports, that usually produce moderating effects on glycemia (Fig. 1).[1,10] In a first phase, the main sources of energy for prolonged aerobic exercise are carbohydrates and lipids derived from within the muscle cells but also from other organs such as the adipose tissue stores and liver. Carbohydrates ingested during physical activity are particularly more useful as its intensity increase, the same being true regarding exercise duration. During prolonged exercise, the presented sources act to rapidly restore circulating glucose levels and to maintain normoglycemia.[11-12] But how does this happen?

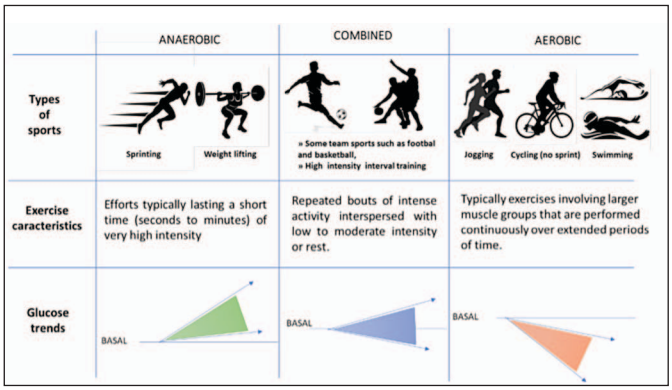

Figure 1. Blood glucose trends according to different types of exercise in type 1 diabetic patients.
Adapted from: Riddell MC, *et al*. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;5:377-90; Mascarenhas LP. Physical exercise in type 1 diabetes: recommendations and care. Rev Educ Física. 2016;22: 223-30.[1,2]

In healthy individuals, blood glucose is maintained within a tight range (70-110 mg/dL) regardless of exercise type (aerobic or anaerobic). In these persons, the reduction in glycemic levels induced by muscle cell glucose uptake during exercise is effectively counteracted by several neuroendocrine mechanisms.[13] The first of them - activated when blood glucose drops to less than 80 mg/dL - is the reduction of insulin secretion. As glycemia progressively decreases, this is followed by increased secretion of glucagon, epinephrine, norepinephrine, growth hormone and cortisol.[10] These hormonal changes lead to increased hepatic glucose output due to increased glycogenolysis (breakdown of hepatic glycogen stores) and gluconeogenesis (conversion of non-carbohydrate precursors such as aminoacids, lactate and glycerol into glucose). By balancing the glucose uptake by muscle cells with the subsequently increased hepatic glucose secretion, these metabolic pathways prevent exercise- induced hypoglycemia and promote stable glycemic levels.[14] During prolonged aerobic exercise, the described hormonal response also contributes to increased lipolysis, as non-esterified fatty acids are mobilized from the adipose tissue and used as energy sources, thus sparing blood glucose.[10,14] Unfortunately, T1D patients deviate from this counter-regulatory response because their pancreas cannot regulate insulin levels during and after exercise: plasma insulin levels are often too high for the intensity of a given exercise, ultimately leading to hypoglycemia - the main exercise-related problem in these patients. In addition, exercise increases insulin sensitivity and also non-insulin mediated glucose uptake through the translocation of glucose transporter type-4 (GLUT-4) to the cell membrane while promoting subcutaneous insulin absorption, further lowering plasma glucose.[4,15] Low glucose levels also occur due to an impaired/ absent hyperglycemic response to hypoglycemia (through glucagon production and sympathoadrenal hyperglycemic responses) in T1D patients. In fact, these blunted counterregulatory hormone responses are even more common among young athletes with a hypoglycemia in the 24-48 hours prior to exercise. This "perfect storm" favors the occurrence of repeated hypoglycemia episodes, resulting in hypoglycemia-associated autonomic failure in some patients who do not experience and respond properly to the potentially life-saving warning symptoms.[4,13] These hypoglycemia-related symptoms include sweating, chills, dizziness, palpitations, fatigue, and im-

paired cognitive processing, which ultimately contribute to poor exercise performance. If not treated, low blood sugars are also associated with falls, coma, or even death.[15]

The timing of exercise is also important to predict hypoglycemia. It is known that when it is performed early in the day, a sustained increase in insulin sensitivity is observed for at least 11 hours after the exercise. On the other hand, exercise that is performed late in the day (such as during the afternoon) elicits a biphasic response in insulin sensitivity, with a first peak during the exercise and the second one 7 to 11 hours later (usually overnight, when the child is sleeping). This is obviously a factor of great anxiety for the patient and their family, that can be avoided with a correct management strategy.[10,16]

Despite the main focus in T1D – exercise relationship being on hypoglycemia avoidance, exercise can also be associated with hyperglycemia.[17] One of the causes is physiological stress of competition: by inducing the secretion of cortisol, catecholamines and interleukin 6, promotes insulin resistance and hyperglycemia before and during exercise, resulting in the need of additional insulin. Other players with putative hyperglycemic effect are multiple environmental factors, such as temperature or humidity. It is thought that warm and humid environments tend to elevate blood glucose levels through excessive production of counterregulatory hyperglycemic hormones, an effect that is counterbalanced by increased subcutaneous insulin absorption due to heat-induced vasodilatation. Insufficient insulin administration and/or excessive carbohydrate intake are also two of the main factors related with high blood glucose values during or after exercise.[10,18] Finally, the type of exercise is also important in this context as described above, since anaerobic exercises may promote hyperglycemia. This fact raised increased interest among the research community because it has been hypothesized that the inclusion of anaerobic intervals in aerobic exercise sessions may provide additional protection against hypoglycemia.[19-21]

Practical concepts for therapy management in type 1 diabetes among children and adolescents

Despite being advised to engage in a wide variety of exercises, there are some issues that T1D patients need to address before, during and after exercise. The knowledge of these considerations is important to achieve a healthy lifestyle and exercise safely while avoiding hypoglycemia and hyperglycemia/ketoacidosis.

1. Contraindications for exercise

» Recent episode of severe hypoglycemia

Exercise is contraindicated if the patient had an episode of severe hypoglycemia (blood glucose under 50 mg/dL or hypoglycemia requiring external assistance for correction due to cognitive impairment) within the 24 hours prior to exercise. It is known that the risk of recurrent hypoglycemia is increased in these cases due to a subsequent deterioration of the protective hormonal counterregulation.[22] Those patients with a mild hypoglycemia prior to exercise should be treated before beginning and carefully monitored (with frequent blood glucose checks) during the activity.[4]

» Severe hyperglycemia with elevated levels of ketones

T1D patients presenting blood glucose (BG) levels > 250 mg/dL should check their ketone levels through blood beta-hydroxybutyrate (BOHB) testing. If ketone levels are >1.5 mmol/L or BG > 350 mg/dL, they must not engage in exercise practice but habitual physical activity included in daily routine should be kept. The cause of these alterations needs to be identified (high carbohydrate intake, insulin omission, illness, among others) and rapidly corrected with insulin administration, hydration, and carbohydrate intake if necessary (depending on the cause). Blood ketone levels ≥ 3.0 mmol/L must be evaluated and treated by a qualified health-care professional due to the risk of occurrence of diabetic ketoacidosis.[10]

» Inadequate training or logistics to deal with exercise-related hypoglycemia

Patients with T1D should be proficient in self-monitoring of blood glucose and hypoglycemia correction before starting any type of exercise. Before the activity, they should check their starting glucose concentration (also monitored regularly during and after exercising) and need to carry blood glucose monitoring equipment and carbohydrate snacks to correct hypoglycemia. If these conditions are not met, exercise is not safe in these patients. Additionally, T1D children and adolescents should be encouraged to have some kind of diabetes identification.1 It is also essential that a responsible adult monitor exercise practice of younger children.[4]

» Injuries

Injuries may contribute to higher blood glucose levels in T1D patients as a response to increased catecholamine and cortisol production in this context. Hyperglycemic states delay the recovery from an injury while hypoglycemic states may contribute to falls, increasing the risk of sustained injuries. For these reasons, exercise is not recommended in this setting.[10]

2. Glycemic management prior and during exercise: practical advice

Glycemic responses to the different types, intensities, and duration of exercise present great variability between and within T1D patients. For this reason, blood glucose management is based on frequent glucose self-monitoring, adjustments in the administered insulin doses (both pre-prandial and prandial) and also in the intake of carbohydrates before, during and after exercise (if needed).[1,23] To avoid blood glucose disturbances (mainly hypoglycemia) during and after exercise, some basic rules should be met. The first of them is to initiate exercise within target glycemic control.[24] To achieve this goal, BG levels should always be evaluated in T1D patients before starting exercise. The target range for BG levels prior to this activity is between 90-250 mg/dL, and ketones should be checked when BG >250 mg/dL or if the patient has symptoms of nausea/vomiting (Table 1).[19]

The child/adolescent should always bring fast-acting carbohydrates to the activity and ingest slowly absorbing ones in the hours prior to exercise (to avoid hypoglycemia). These fast-acting carbohydrates taken during exercise should not be accompanied by insulin and are used to stabilize glucose levels in patients in risk of hypoglycemia or to correct it. This is especially important in some particular cases (such as in patients not able to reduce mealtime insulin bolus prior to exercise). The slowly absorbing carbohydrates may be ingested in the hours prior to exercise as part of a meal with insulin, but accounting for the expected insulin dose reductions (Fig. 2).[25]

The site of insulin administration should not be the one that will be exercised (by increasing blood flow to the exercised area,

Table 1. Recommended glucose management strategy before starting an exercise. This strategy intends to stabilize glycemia at the beginning of the exercise, and aerobic exercise will probably demand additional carbohydrates. Glycemia should always be checked regularly during exercise. This plan can be modified based on several factors such as patient`s previous responses to exercise, recent boluses of insulin or the trend arrow on continuous glucose monitoring.

Blood glucose	How to proceed?
<90 mg/dL	Ingest 10-20 g of fast-acting carbohydrates and delay the beginning of exercise until BG>90 mg/dL.
90-125 mg/dL	Consume 10-20 g of fast-acting carbohydrates before starting aerobic exercise.
126-180 mg/dL	Proceed with aerobic or anaerobic exercise. The patient should ingest supplemental carbohydrates after beginning exercise if it lasts for more than 30 minutes.
181-250 mg/dL	Proceed with aerobic or anaerobic exercise.
>250 mg/dL	**Measure ketones:** **BOHB ≥3.0 mmol/L:** Exercise is contra-indicated. Look for a qualified health-care professional due to the risk of diabetic ketoacidosis. **BOHB ≥1.5-2.9 mmol/L:** Exercise is contra-indicated. Give ½ correction dose of insulin with pen/syringe. Follow sick-day rules to manage hyperglycemia/ketosis. **BOHB 1.1-1.4 mmol/L:** Give ½ correction dose of insulin with pen/syringe, wait 60 minutes after correction and proceed exercise only after ensuring decreased BG. **BOHB 0.6-1.0 mmol/L:** Give ½ correction dose of insulin with pen/syringe, wait 15 minutes after correction and proceed exercise. **BOHB <0.6 mmol/L:** Ok to proceed exercise

Adapted from: 1. Riddell MC, *et al*. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;5:377-90; Adolfsson P, *et al*. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. Pedi atr Diabetes. 2018;19:205-26; Colberg SR, *et al*. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016;39:2065-79.[1,4,19]

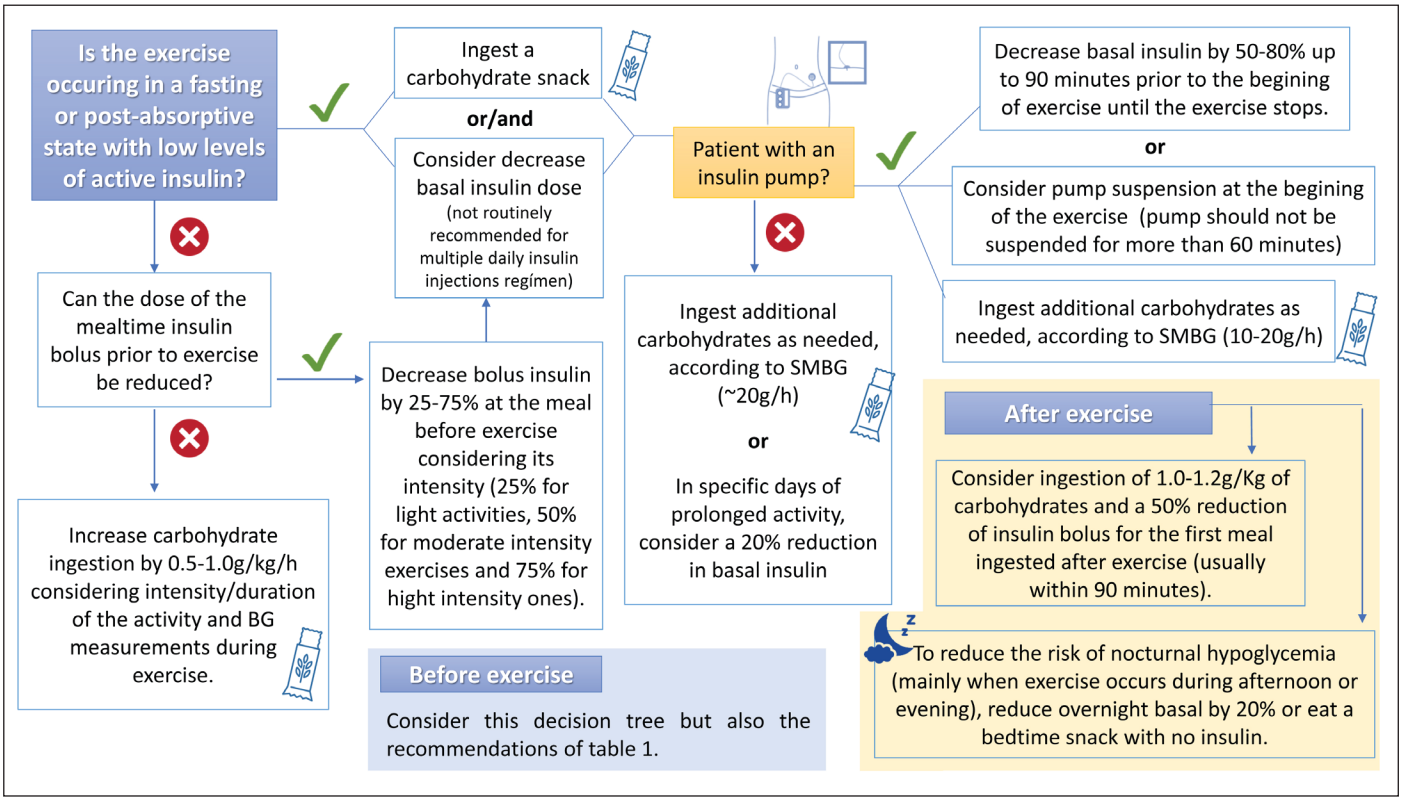

Figure 2. Decision tree for type 1 diabetes management before, during and after exercise.
Adapted from: Riddell MC, *et al*. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;5:377-90; Mascarenhas LP. Physical exercise in type 1 diabetes: recommendations and care. Rev Educ Física. 2016;22: 223-30.[1,2]
SMBG: Self-monitoring blood glucose; BG: Blood glucose

it will also increase insulin absorption and favor hypoglycemia occurrence).[26] In the case of prolonged exercise, the patient needs to increase the intensity/ duration of the exercise progressively and consider the introduction of solid or liquid carbohydrates before, during and after the activity. In addition, when the physical activity is planned to be performed at the time of insulin peak

action, its dose should be reduced. The patient or his family also need to make others aware of the procedures regarding a severe hypoglycemia.[1,27] In patients with continuous glucose monitoring, the alerts regarding low glucose values (and low glucose suspend mode in newer pumps) may be also a valuable tool to avoid exercise-related hypoglycemia.[28] Finally, the BG value measured before bedtime on the evening after relevant physical activity should be evaluated; slow-absorbing extra- carbohydrates should be added at bedtime and/or basal insulin should be reduced to avoid nocturnal hypoglycemia (usually when the patient is asleep).[29]

It should also be stressed the importance of patients and their families having access to simple and written information regarding the procedures to be carried out before, during and after exercise. This will a be precious help to avoid glycemic disturbances related with exercise, that are many times associated with patient frustration or even exercise abandonment.[30,31] In addition, monitoring blood glucose before, during and after exercise is of great importance to adjust the therapeutic approach and promote exercise practice with less glycemic disturbances.[1,4]

One of the factors influencing the therapeutic approach is the timing of exercise in relation to the last meal. If the exercise is occurring in a fasting or pos-absorptive state with low levels of insulin, the patient should take a snack or/and consider decreasing the dose of basal insulin (in the case of insulin pumps, the basal rate infusion can be reduced in 50%-80% up to 90 minutes prior to the beginning of exercise or even be suspended temporarily). If the exercise is occurring postprandially, the insulin bolus of that previous meal should be reduced between 25% and 75% taking into account the intensity of the exercise (greater reductions for higher intensity exercises). If this previous meal is already taken with insulin, the patient should ingest carbohydrates by 0.5-1.0 g/kg/h according to intensity/duration of the activity and BG measurements. After exercise, the patient should consider the ingestion of 1.0-1.2 g/kg/ of carbohydrates and a 50% reduction of insulin bolus for the first meal ingested after exercise. Nocturnal hypoglycemia can be avoided by reducing overnight basal by 20% or by eating a snack at bedtime with no insulin.[1,4] Fig. 2 displays a proposed decision tree which must be taken into consideration to help these patients to successfully manage their glycemic profile while practicing exercise and with increased relevance in situations of prolonged exercise (more than 30 minutes).

It is important to understand that these recommendations are just a starting point and that every individual with diabetes is unique. For this reason, the effect of every modification in insulin dose or carbohydrate change should be carefully evaluated and adapted taking into account the patient`s needs. Thus, BG monitoring plays a central role in this process by allowing the identification of metabolic adaptations and appropriate interventions. After the adaptation period to these new situations (with eventual understanding of glucose patterns related with that particular type of exercise), monitoring follows the recommendations already mentioned in the paper. The increasingly used continuous glucose monitoring devices (CGMs) are also a major breakthrough to help these patients maintaining normoglycemia. These devices measure glucose in the interstitial fluid, providing real-time sensor glucose data, and some of them are equipped with alarms for hyper and hypoglycemia, which is reassuring for patients and their families. For children and adolescents that will exercise, the alarms of hypo and hyperglycemia alarms should be set at 100 mg/dL and 180 mg/dL (giving time to the patient to address the problem properly), or individualized if required. Despite the great advantages in glucose pattern identification and diabetes control, a self-monitored confirmatory blood glucose should be performed in glycemic extremes (hypo and marked hyperglycemia) or when the symptoms do not add up with the glycemic value provided by CGM. In addition, a lag time exists between the glucose value in the vasculature and in the interstitial fluid. A consensus statement regarding CGM monitoring for exercise among individuals with type 1 diabetes was published recently and addresses this issue in more detail.[33]

Lastly, it should be addressed that there is a lack of evidence regarding exercise management among pediatric patients (when compared with adult ones). For this reason, the authors would like to draw attention for the fact that some recommendations followed nowadays regarding pediatric patients in this context might be based in adult ones. This stresses the importance of more research dedicated to this particular issue.

Conclusion

Physical activity is a fundamental pillar in controlling diabetes, in addition to having multiple other benefits.[32] Precisely for this reason, it is necessary that the follow-up teams of children and young people with T1DM know how to deal with the challenges of exercising, in order to help patients and their families. In this way, it will be avoided that potentially demotivating situations arise and that contribute to the abandonment of such an important activity. The knowledge of the glycemic impact of different types of exercise (anaerobic, aerobic and combined) and exercise physiology is important to predict glycemic trends and to understand how a particular exercise affect glycemic control. This can be effectively measured with glucometers or with new CGM devices, that provide valuable information to the patient but also to the physician. The main therapeutic approaches usually encompass insulin dose reductions and/or carbohydrate ingestion (according to the monitored glycemia), aiming to the maintenance of normoglycemia during this important activity.

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FM - conceptualization, writing and review.
SF,CC,SBS,CC- conceptualization and review.

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References / Referências

1. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;5:377-90. doi:10.1016/s2213-8587(17)30014-1
2. Mascarenhas LP. Physical exercise in type 1 diabetes: recommendations and care. Rev Educ Física. 2016;22: 223-30.
3. Ostman C, Jewiss D, King N, Smart NA. Clinical outcomes to exercise training in type 1 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2018;139:380-91. doi:10.1016/j.diabres.2017.11.036
4. Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan F, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. Pediatr Diabetes. 2018;19:205-26. doi: 10.1111/pedi.12755.
5. Ryninks K, Sutton E, Thomas E, Jago R, Shield JPH, Burren CP. Attitudes to Exercise and Diabetes in Young People with Type 1 Diabetes Mellitus: A Qualitative Analysis. PloS One. 2015;10:e0137562. doi:10.1371/journal.pone.0137562
6. Chetty T, Shetty V, Fournier PA, Adolfsson P, Jones TW, Davis EA. Exercise Management for Young People With Type 1 Diabetes: A Structured Approach to the Exercise Consultation. Front Endocrinol. 2019;10:326-6. doi:10.3389/fendo.2019.00326
7. Chowdhury S. Puberty and type 1 diabetes. Indian J Endocrinol Metab. 2015;19:S51-S54. doi:10.4103/2230-8210.155402
8. Zaharieva DP, Riddell MC. Prevention of exercise-associated dysglycemia: a case study–based approach. Diabetes Spect. 2015;28:55-62. doi:10.2337/diaspect.28.1.55
9. Patel H, Alkhawam H, Madanieh R, Shah N, Kosmas CE, Vittorio TJ. Aerobic vs anaerobic exercise training effects on the cardiovascular system. World J Cardiol. 2017;9:134-8. doi: 10.4330/wjc.v9.i2.134
10. Riddell MC. Management of exercise for children and adolescents with type 1 diabetes mellitus. UpTodate; 2021. [accessed May 25, 2021]. Available from: https://www.uptodate.com/contents/management-of-exercise-for-children-and-adolescents-with-type-1-diabetes-mellitus
11. Riddell MC. The endocrine response and substrate utilization during exercise in children and adolescents. J Appl Physiol. 2008;105:725-33. doi: 10.1152/japplphysiol.00031.2008.
12. Riddell MC, Bar-Or O, Hollidge-Horvat M, Schwarcz HP, Heigenhauser GJ. Glucose ingestion and substrate utilization during exercise in boys with IDDM. J Appl Physiol. 2000;88:1239-46. doi:10.1152/jappl.2000.88.4.1239
13. Cockcroft EJ, Narendran P, Andrews RC. Exercise-induced hypoglycaemia in type 1 diabetes. Exp Physiol. 2020;105:590-9. doi:10.1113/ep088219
14. Codella R, Terruzzi I, Luzi L. Why should people with type 1 diabetes exercise regularly? Acta Diabetol. 2017;54:615-30. doi:10.1007/s00592-017-0978-x
15. Farinha JB, Krause M, Rodrigues-Krause J, Reischak-Oliveira A. Exercise for type 1 diabetes mellitus management: General considerations and new directions. Med Hypotheses. 2017;104:147-53. doi:10.1016/j.mehy.2017.05.033
16. Pivovarov JA, Taplin CE, Riddell MC. Current perspectives on physical activity and exercise for youth with diabetes. Pediatr Diabetes. 2015;16:242-55. doi:10.1111/pedi.12272
17. Riddell MC, Iscoe KE. Physical activity, sport, and pediatric diabetes. Pediatric diabetes. Feb 2006;7(1):60-70. doi:10.1111/j.1399-543X.2006.00146.x
18. Galassetti P, Riddell MC. Exercise and type 1 diabetes (T1DM). Comprehensive Physiology. Jul 2013;3(3):1309-36. doi:10.1002/cphy.c110040
19. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016;39:2065-79. doi: 10.2337/dc16-1728.
20. Yardley JE, Sigal RJ, Perkins BA, Riddell MC, Kenny GP. Resistance exercise in type 1 diabetes. Can J Diabetes. 2013;37:420-6. doi: 10.1016/j.jcjd.2013.07.020.
21. Hasan S, Shaw SM, Gelling LH, Kerr CJ, Meads CA. Exercise modes and their association with hypoglycemia episodes in adults with type 1 diabetes mellitus: a systematic review. BMJ Open Diabetes Res Care. 2018;6:e000578. doi: 10.1136/bmjdrc-2018-000578.
22. Ertl AC, Davis SN. Evidence for a vicious cycle of exercise and hypoglycemia in type 1 diabetes mellitus. Diabetes Metab Res Rev. 2004;20:124-30. doi: 10.1002/dmrr.450.
23. Tran BD, Galassetti P. Exercise in pediatric type 1 diabetes. Pediatr Exerc Sci. 2014;26:375-83. doi: 10.1123/pes.2014-0066.
24. Diabetes Canada Clinical Practice Guidelines Expert Committee, Sigal RJ, Armstrong MJ, Bacon SL, Boulé NG, Dasgupta K, et al. Physical Activity and Diabetes. Can J Diabetes. 2018;42:S54-S63. doi: 10.1016/j.jcjd.2017.10.008.
25. Scott S, Kempf P, Bally L, Stettler C. Carbohydrate Intake in the Context of Exercise in People with Type 1 Diabetes. Nutrients. 2019;11 :3017. doi:10.3390/nu11123017
26. Pitt JP, McCarthy OM, Hoeg-Jensen T, Wellman BM, Bracken RM. Factors Influencing Insulin Absorption Around Exercise in Type 1 Diabetes. Front Endocrinol. 2020;11:573275. doi: 10.3389/fendo.2020.573275.
27. Colberg SR. Key Points from the Updated Guidelines on Exercise and Diabetes. Opinion. Front Endocrinol. 2017;8:33. doi:10.3389/fendo.2017.00033
28. Abraham MB, Davey R, O'Grady MJ, Ly TT, Paramalingam N, Fournier PA, et al. Effectiveness of a Predictive Algorithm in the Prevention of Exercise-Induced Hypoglycemia in Type 1 Diabetes. Diabetes Technol Ther. 2016;18:543-50. doi: 10.1089/dia.2016.0141.
29. Campbell MD, Walker M, Bracken RM, Turner D, Stevenson EJ, Gonzalez JT, et al. Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: a randomized controlled trial. BMJ Open Diabetes Res Care. 2015;3:e000085. doi: 10.1136/bmjdrc-2015-000085.
30. Pinsker JE, Kraus A, Gianferante D, Schoenberg BE, Singh SK, Ortiz H, et al. Techniques for Exercise Preparation and Management in Adults with Type 1 Diabetes. Can J Diabetes. 2016;40:503-8. doi: 10.1016/j.jcjd.2016.04.010.
31. Lascar N, Kennedy A, Hancock B, Jenkins D, Andrews RC, Greenfield S, et al. Attitudes and barriers to exercise in adults with type 1 diabetes (T1DM) and how best to address them: a qualitative study. PLoS One. 2014;9:e108019. doi: 10.1371/journal.pone.0108019.
32. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. Diabetologia. 2012;55:542-51. doi:10.1007/s00125-011-2403-2
33. Moser O, Riddell MC, Eckstein ML, Adolfsson P, Rabasa-Lhoret R, van den Boom L, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDRF and supported by the American Diabetes Association (ADA). Pediatr Diabetes. 2020 ;21:1375-93. doi: 10.1111/pedi.13105.

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Artigo Revisão

Paralisia Hipocaliémica Periódica Secundária: Uma Revisão da Literatura

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INFORMAÇÃO SOBRE O ARTIGO

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Paralisia Hipocaliémica Periódica/etiologia.

R E S U M O

As paralisias periódicas correspondem a um grupo de doenças neuromusculares que ocorrem por afeção dos canais iónicos do músculo esquelético. Os autores deste artigo decidiram agrupar as formas de paralisia periódica consoante os níveis séricos de potássio concomitantes: paralisia periódica hipercaliémica, paralisia periódica normocaliémica e paralisia periódica hipocaliémica.
Clinicamente as paralisias hipocaliémica periódicas caracterizam-se pelo aparecimento súbito e transitório de fraqueza muscular, geralmente proximal e simétrica, iniciando pelos membros inferiores e progredindo para os membros superiores. Os episódios agudos podem ser precedidos por um período prodrómico constituído por mialgias e espasmos musculares. A duração dos episódios de paralisia varia de caso para caso, podendo durar alguns minutos ou vários dias. A maioria apresenta resolução espontânea, no entanto, em depleções de potássio graves, a tetraparesia aguda é mais marcada podendo culminar na tetraplegia e morte por insuficiência dos músculos respiratórios e/ou arritmias fatais. A manifestação laboratorial cardinal é um potássio sérico inferior a 3,5 mmol/L, embora geralmente seja muito inferior.
A maioria dos casos de paralisia periódica são hereditários, existindo, no entanto, causas secundárias de paralisia periódica. Estas ocorrem conceptualmente por quaisquer alterações na distribuição transcelular de potássio, absorção ou eliminação (renal ou extra-renal). Neste artigo realizamos uma revisão teórica da literatura publicada até à data das causas secundárias de paralisia hipocaliémica periódica.

Keywords:
Hypokalemic Periodic Paralysis/diagnosis;
Hypokalemic Periodic Paralysis/etiology.

Secondary Hypokalemic Periodic Paralysis: A Review of Literature

A B S T R A C T

Periodic paralysis corresponds to a group of neuromuscular disorders that occur due to the affection of the ion channels of the skeletal muscle. The authors of this article decided to group the forms of periodic paralysis according to the concomitant serum potassium levels: hyperkalaemic periodic paralysis, normokalaemic periodic paralysis and hypokalaemic periodic paralysis.
Clinically, periodic hypokalaemic paralysis is characterized by the sudden and transient appearance of muscle weakness, usually proximal and symmetrical, starting in the lower limbs and progressing to the upper limbs. Acute episodes may be preceded by a prodromal period consisting of myalgias and muscle spasms. The duration of episodes of paralysis varies from case to case, and may last a few minutes or several days. Most have a spontaneous resolution, however, in severe potassium depletion, acute tetraparesis is more marked and may culminate in tetraplegia and death from respiratory muscle failure and/or fatal arrhythmias. The cardinal laboratory manifestation is a serum

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potassium of less than 3.5 mmol/L, although it is usually much lower.
Most cases of periodic paralysis are hereditary, although there are secondary causes of periodic paralysis. These conceptually occur by any changes in the transcellular distribution of potassium, absorption, or elimination (renal or extra-renal). In this article, we perform a review of the published literature to date of secondary causes of periodic hypokalaemic paralysis.

Introdução

As paralisias periódicas (PP) correspondem a um conjunto de doenças neuromusculares que ocorrem por afeção dos canais iónicos - potássio, cálcio ou sódio - do músculo esquelético. Na bibliografia estão descritas várias classificações das PP. Os autores deste artigo decidiram agrupar as formas de PP consoante os níveis séricos de potássio concomitantes: paralisia periódica hipercaliémica, paralisia periódica normocaliémica e paralisia periódica hipocaliémica. Algumas doenças, como é o caso da síndrome de Andersen-Tawil, cursam com níveis séricos de potássio variáveis, não se incluindo em nenhum dos grupos descritos (Fig. 1).[1,2]

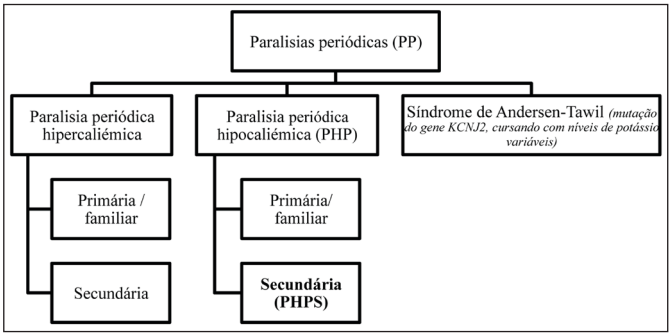


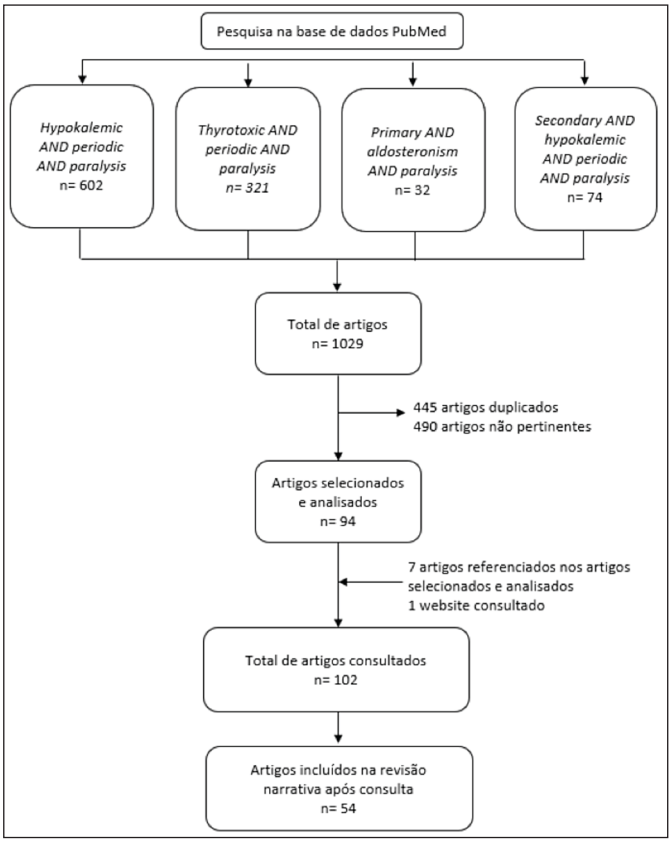
Figura 1. Divisão das paralisias periódicas.

A maioria dos casos de PP são hereditários, ainda que raros, com uma prevalência de 1/100 000. São maioritariamente doenças de transmissão autossómica dominante, embora em 1/3 possam ser esporádicas, causadas por mutações em genes que codificam as subunidades das proteínas constituintes de canais iónicos presentes nas células musculares, com consequente alteração da função contráctil. Manifestam-se sobretudo em homens caucasianos nas duas primeiras décadas de vida.[3,4]

No entanto, existem causas secundárias de PP que ocorrem conceptualmente por quaisquer alterações na distribuição transcelular de potássio, absorção ou eliminação (renal ou extra-renal).

Métodos

Neste artigo realizamos uma revisão narrativa da literatura publicada até à data das causas secundárias de paralisia hipocaliémica periódica. Foi realizada uma pesquisa da literatura publicada na base de dados *PubMed*, entre dezembro de 2021 e maio de 2022, com as palavras chave, "*hypokalemic AND periodic AND paralysis*", "*thyrotoxic AND periodic AND paralysis*", "*primary AND aldosteronism AND paralysis*" e "*secondary AND hypokalemic AND periodic AND paralysis*". A pesquisa foi restrita a artigos escritos em inglês, português e espanhol. Foram incluídas revisões clássicas, sistemáticas e artigos originais como estudos observacionais transversais ou longitudinais, retrospetivos ou prospetivos sobre o tema. Foram excluídos artigos com data de publicação anterior ao ano de 2000. Após leitura do título e resumo, foram selecionados e analisados 94 artigos. Foram adicionalmente selecionados 7 artigos referenciados devido à sua relevância e consultado um website de informação médica (*UpToDate, Inc.*) – Fluxograma 1.



Fuxograma 1. Métodos.

Manifestações Clínicas

A paralisia hipocaliémica periódica (PHP) apresenta um leque variável de manifestações clínicas. Nos casos mais ligeiros poderá manifestar-se apenas por uma diminuição ligeira da força muscular transitória. Nos casos mais graves pode existir paralisia aguda grave, com comprometimento cardiovascular associado. Afeta sobretudo o sistema neuromuscular, embora também existam repercussões noutros sistemas, como o cardiovascular ou o gastrointestinal.

Classicamente manifesta-se pelo aparecimento súbito e transitório de fraqueza muscular, geralmente dos grupos musculares proximais e de forma simétrica, com início nos membros inferiores e posterior progressão para os membros superiores. Geralmente os episódios agudos são precedidos por um período prodrómico constituído por mialgias e espasmos musculares, que podem ser precipitados pela ingestão de refeições ricas em hidratos de carbono ou após exercício físico vigoroso. Estão descritos outros precipitantes menos comuns, como o trauma, exposição ao frio, infeção, menstruação ou a utilização de fármacos como diuréticos, insulina ou corticosteróides.[5]

A duração dos episódios de paralisia varia de caso para caso, podendo durar alguns minutos ou vários dias. A maioria apresenta resolução espontânea,[6] no entanto, em situações com importantes depleções de potássio, a tetraparesia aguda é mais grave, podendo

culminar em casos de tetraplegia ou morte por insuficiência dos músculos respiratórios e/ou arritmias fatais.[7]

No exame físico, para além da diminuição de força segmentar e global, objetiva-se uma diminuição ou ausência de reflexos osteotendinosos. As sensibilidades motora e sensitiva não estão alteradas.[4]

Um potássio sérico inferior a 3,5 mmol/L é a manifestação laboratorial cardinal das PHP, embora geralmente se encontre bastante baixo. Na paralisia hipocaliémica periódica familiar os níveis de potássio entre crises são normais, o que as distingue das paralisias hipocaliémica periódicas secundárias (PHPS), onde geralmente se verifica uma hipocaliémia mantida. Alterações eletrocardiográficas são comuns (tais como depressão do segmento ST, o achatamento e inversão das ondas T, aparecimento das ondas U e prolongamento do intervalo QT) mas não estão correlacionadas com a gravidade das manifestações neuromusculares.[4,8]

Relembrar que existem várias patologias com elevada morbi-mortalidade que se apresentam com tetraparesia aguda, sendo o seu reconhecimento crucial para uma gestão adequada e tratamento oportuno (Tabela 1).

Tabela 1. Diagnóstico diferencial na tetraparésia aguda não traumática.

Causas de tetraparesia aguda não traumática	
Neurológicas	Acidente vascular cerebral (eventos da circulação posterior ou isquemia medular), esclerose múltipla, mielinólise pôntica, mielite transversa, compressão medular (abcesso, neoplasia, hemorragia), doenças do neurónio periférico como síndrome de Guillain-Barre, doenças da junção neuro-muscular como a miastenia gravis ou síndrome de Lambert-Eaton
Metabólicas / tóxicas	Anormalidades eletrolíticas (hipocaliémia severa, hipomagnesémia, hipofosfatémia); hipoglicémia severa, doenças endócrinas (hipertiroidismo ou hipotiroidismo), porfirias, fármacos (opiáceos, antagonistas dos canais de cálcio, aminoglicosídeos, clindamicina) e tóxicos (álcool, organofosforados, arsénio, venenos de algumas espécies de cobras e aranhas)
Infeciosas / inflamatórias	Poliomielite aguda, difteria, botulismo, polimiosite, dermatomiosite, miopatia inflamatória aguda (viral, parasitária ou auto-imune como no síndrome anti-sintetase ou miopatia necrotizante imuno-mediada), neuropatia vasculítica (primária ou secundária), miopatia dos cuidados intensivos, síndromes paraneoplásicos
Doenças neuropsiquiátricas	Cataplexia, narcolepsia, fibromialgia, síndrome da fadiga crónica, síndrome de Munchausen

Homeostase do potássio

O potássio é um ião predominantemente intracelular (98% do potássio é intracelular) que desempenha um papel essencial à função celular em todos os nossos órgãos e sistemas. A concentração sérica de potássio normal oscila entre 3,5-5,3 mEq/L. Existem vários canais iónicos responsáveis pela homeostase deste ião, os principais são a bomba Na+K+ ATPase e o *inwardly rectifying potassium channel* (Kir), que garantem a manutenção de um gradiente intracelular positivo (K+ intracelular > K+ extracelular). A Na+K+ ATPase é a principal bomba responsável pelo influxo celular de potássio e canal Kir é o principal responsável pelo efluxo celular de potássio. O músculo esquelético depende deste gradiente para desempenhar a sua função motora pelo que a redução da concentração de potássio extracelular leva a uma hiperpolarização da membrana celular, inativação do sarcolema e consequente diminuição da força muscular.[10-13]

Conceptualmente, qualquer causa de hipocaliemia severa poderá cursar com PHP (Tabela 2). No entanto, existem causas de hipocaliémia que se encontram mais associadas a PHP do que outras. Esta associação deve-se sobretudo ao carácter insidioso destas entidades que conduzem a uma descida progressiva e silenciosa de potássio. Adicionalmente o atraso no diagnóstico conduz à manifestação clínica tardia e exuberante da paralisia (Tabela 3).

Tabela 2. Principais causas de hipocaliemia.

Principais causas de hipocaliemia	
***Shift* transcelular de potássio**	Alcalose, hipotermia, paralisia periódica hipocaliémica familiar, tireotoxicose, hiperproliferação celular (anemia megaloblástica, leucemias) fármacos (insulina, B2 agonistas, teofilina, verapamil, intoxicação por cloroquina, quetiapina ou risperidona), intoxicação por bário.
Perdas renais	Diuréticos de ansa, tiazídicos, inibidores da anidrase carbónica (acetazolamida), hipomagnesémia, acidose tubular renal (tipo I / distal ou tipo II / proximal), poliúria (pós-obstrutiva, diurese osmótica na diabetes descompensada, administração de manitol), excesso de mineralocorticoídes (hiperaldosteronismo primário ou secundário), hipercortisolismo (síndrome de Cushing), hiper-reninismo (estenose da artéria renal ou tumor produtor de renina), fármacos (penicilina G, aminoglicosídeos, anfotericina B), doenças tubulares hereditárias (síndrome de Gitelman, Bartter e Liddle)
Perdas extra-renais	Perdas gastrointestinais: vómitos, diarreia, uso abusivo de laxantes/ preparação para exames endoscópicos, drenagens naso-gástricas, fístulas gastro-intestinais, adenoma viloso do cólon, síndome de Zollinger-Ellison Outras perdas: diálise, plasmaferese, sudorese profusa, queimaduras extensas
Défice de absorção	Baixa ingesta, alimentação parentérica com baixa reposição de potássio, défice de absorção (resseções segmentares extensas do intestino; *Tropical sprue*)

Tabela 3. Causas mais comuns de hipocaliemia que cursam com paralisia hipocaliémica periódica. A paralisia periódica tireotóxica é a causa secundária mais comum.

Causas mais comuns de paralisia hipocaliémica periódica	
***Shift* transcelular de potássio**	Paralisia periódica hipocaliémica familiar (+ comum) Tireotoxicose (paralisia hipocaliémica tireotóxica) (secundária + comum) Intoxicação por bário
Perdas renais	Excesso de mineralocorticoídes (hiperaldosteronismo primário ou secundário) Hipercortisolismo (síndrome de Cushing) Síndrome de Sjogren Doenças tubulares hereditárias (síndrome de Gitelman, Bartter e Liddle) Acidose tubular renal tipo I e outras acidoses tubulares
Perdas extra-renais	PDoença celíaca Síndrome do intestino curto Síndrome de Zollinger-Ellison *Tropical sprue*

Doenças Endócrinas

Paralisia periódica tireotóxica

A paralisia periódica tireotóxica (PPT) é uma complicação rara, mas potencialmente fatal, de um estado de tireotoxicose.[7] Classicamente cursa com hipocaliémia durante os episódios agudos, sendo a etiologia mais frequente de PHPS.[10,15]

É mais comum em indivíduos de origem asiática (2% *vs* 0,1%-0,2% em caucasianos) correspondendo estes a 90% de todos os casos relatados na literatura.[4,16] No Japão, a incidência de PPT em doentes

com hipertiroidismo é de 1,9%-6,2%.[17] Apesar do hipertiroidismo ser mais frequente no sexo feminino, a PPT é mais frequente no sexo masculino (rácio 20:1).[9,18] A maioria dos casos são esporádicos, não existindo história familiar. A doença de Graves, por ser a etiologia mais comum de hipertiroidismo, é a causa que mais frequentemente se associa a PPT mas qualquer causa de tireotoxicose, incluindo a administração de quantidades excessivas de hormona tiroideia, pode desencadear episódios de PPT em pacientes suscetíveis.[7,19]

O episódio inaugural de PPT surge habitualmente entre os 20 e os 40 anos. Cerca de metade dos doentes com PPT não apresentam sintomas relacionados com o hipertiroidismo na altura em que surgem os primeiros sintomas neuromusculares.[7]

O mecanismo exato da PPT permanece desconhecido, existindo vários fatores que contribuem para a hipocaliémia e paralisia. Um dos pilares da fisiopatologia da PPT é a sobre estimulação da bomba Na+K+ ATPase pelo ambiente tireotóxico. As hormonas tiroideias promovem a atividade desta bomba iónica por mecanismos genómicos, através do aumento do gene codificador da Na+K+ ATPase e por mecanismos não-genómicos, através da promoção da atividade intrínseca da bomba iónica e sua inserção na membrana celular. Agonistas β2 adrenérgicos estimulam as bombas iónicas através da amplificação da produção intracelular de cAMP. Adicionalmente, os episódios de PPT encontram-se associados a um estado de hiperinsulinémia. A insulina induz o influxo celular de potássio através da promoção da atividade intrínseca da bomba Na+K+ ATPase. O facto da PPT ser mais comum em homens apesar do hipertiroidismo ser mais frequente em mulheres leva a que alguns autores sugiram um potencial papel dos androgénios na atividade da bomba Na+K+ ATPase.[10-13,16]

A atividade do canal Kir encontra-se reduzida em doentes com PPT.[13] Adicionalmente, a insulina e as catecolaminas para além de ativarem a bomba Na+K+ ATPase inibem a Kir.[12] Múltiplos estudos reportam que mutações que inativem o gene que codifica a bomba Kir2.6, um canal iónico Kir presente no músculo esquelético, se associam a PPT e aumentam a sua probabilidade de recorrência.[20-22] Portanto, um estado tireotóxico promotor de uma inativação da Kir conjugado com sobre ativação da Na+K+ ATPase pode precipitar hipocaliémia importante e consequente paralisia.

A terapêutica em fase aguda tem como objetivo normalizar os níveis séricos de potássio e reverter a paralisia associada. Classicamente a terapêutica inicial passa pela administração endovenosa de potássio com o objetivo de rapidamente normalizar a caliémia e prevenir arritmias cardíacas e falência respiratória, as principais causas de morte associadas a esta condição.[22] Na PPT, a hipocaliémia é secundária a uma redistribuição celular iónica anormal e não a um défice total de potássio. Esta é a razão pela qual 40%-70% dos doentes apresentam hipercaliémia iatrogénica uma vez restituída a homeostase iónica. A gravidade da hipercaliémia apresenta uma relação direta com a dose de potássio administrada e a sua velocidade de administração.[23,24] Para além da suplementação com potássio, alguns autores defendem a utilização de beta-bloqueantes em fase aguda, como é o caso do propanolol endovenoso, particularmente útil quando a hipocaliémia é refratária à administração inicial de potássio.[11,22]

A terapêutica definitiva da PPT depende da etiologia e gravidade do hipertiroidismo em causa. Um controlo adequando da função tiroideia reduz drasticamente o risco de novos episódios. Para prevenção de recidiva, no período entre episódios estão recomendados beta-bloqueantes pela sua capacidade de inibir a bomba Na+K+ ATPase, bem como evicção de fatores precipitantes. Não está recomendada suplementação oral com potássio para prevenção de novos episódios, uma vez que a caliémia se encontra habitualmente normal.[11,22]

Hiperaldosteronismo Primário

O hiperaldosteronismo primário é caracterizado pela produção independente e inapropriadamente excessiva de aldosterona pelo córtex das glândulas suprarrenais. Aproximadamente 95% dos casos esporádicos de hiperaldosteronismo primário são causados por um adenoma produtor de aldosterona ou hiperplasia das suprarrenais.

Clinicamente, o hiperaldosteronismo primário cursa com hipertensão arterial, hipervolémia, hipocaliémia e alcalose metabólica. A hipertensão arterial encontra-se presente em 90% dos doentes, a hipocaliémia em 9%-37% e a alcalose metabólica em 1%-2% dos casos.[25,26] A PHPS está presente em 20,4%-42% dos casos de hiperaldosteronismo primário, estando principalmente associada a adenomas produtores de aldosterona, uma vez que é mais provável cursarem com hipocaliemias graves do que os casos de hiperplasia das suprarrenais.[17,27]

As manifestações clínicas do hiperaldosteronismo primário devem-se, principalmente, à ação renal da aldosterona. Esta, promove a ativação da bomba Na+K+ presente nas células dos tubos distal e coletor do nefrónio, através da sua ligação aos recetores mineralocorticóides. Desta ativação resulta um aumento da reabsorção renal de sódio e um aumento da excreção renal de potássio.

A hipocaliémia verificada no hiperaldosteronismo primário deve-se a um défice global de potássio e pode ser grave o suficiente para precipitar um episódio de paralisia aguda.[28] Na terapêutica de um episódio agudo de PHPS secundária a hiperaldosteronismo primário, ao contrário da PPT, o aporte de potássio deverá ser superior, uma vez que o risco de hipercaliémia iatrogénica é bastante menor. O tratamento definitivo da condição é a excisão cirúrgica da suprarrenal envolvida, nos casos unilaterais. Como ponte até à cirurgia ou nos casos em que a mesma não é possível, antagonistas dos recetores mineralocorticóides com ou sem suplementação de potássio são alternativas.[6,29,30]

Pseudohiperaldosteronismo

O pseudohiperaldosteronismo corresponde a um grupo heterogéneo de condições cuja clínica se assemelha ao hiperaldosteronismo, nomeadamente hipertensão arterial, hipocaliémia e alcalose metabólica. No entanto, laboratorialmente os níveis séricos de aldosterona e atividade de renina encontram-se diminuídos. À semelhança do hiperaldosteronismo, também as várias etiologias de pseudohiperaldosteronismo se associam a PHPS.[31]

A ingestão de alcaçuz ou seus derivados é uma causa conhecida de pseudohiperaldosteronismo. Este agente inibe a enzima 11β-hidroxiesteroide desidrogenase, impedindo a inativação do cortisol em cortisona, permitindo a ligação do cortisol aos recetores mineralocorticóides e a tua ativação. Estão descritos casos de PHPS em doentes com consumo pontual ou crónico de alcaçuz.[4,31]

A síndrome de Liddle corresponde a uma doença autossómica dominante de elevada penetrância que se apresenta sob a forma de pseudoaldosteronismo. A doença é causada por mutações com ganho de função de pelo menos um dos genes *SCNN1A*, *SCNN1B* e *SCNN1G* que codificam as subunidades do canal iónico ENaC. Este canal desempenha um papel central na homeostase do sódio, estando presente em células epiteliais do rim. Na doença de Liddle, a mutação com ganho de função causa um aumento da reabsorção renal de sódio, o que se traduz numa clínica semelhante ao hiperaldosteronismo.[31]

São outras causas conhecidas de pseudohiperaldosteronismo o consumo excessivo de agentes mineralocorticóides, como a fludrocortisona, síndrome de Cushing ou terapêutica crónica com corticosteróides, défices enzimáticos das enzimas 11β-hidroxiesteroide desidrogenase ou 17α-hidroxiesteroide desidrogenase ou o consumo crónico de toranja.[31]

Hiperinsulinismo

Conceptualmente, é possível que o hiperinsulinismo seja um fator de predisposição para PHP no geral, uma vez que a insulina é ativadora da bomba Na+-K+ ATPase e, por isso, promotora de hipocaliémia. Lanzi R *et al* descrevem um caso de PHPS secundária a um défice adquirido de hormona do crescimento. Colocam como justificação mais provável a de que o estado de hiperinsulinémia em associação com o défice de hormona do crescimento promove um aumento da atividade intrínseca da bomba Na+-K+ ATPase e consequente PHP.[32,33]

Doenças renais

A excreção renal de potássio ocorre sobretudo através das células principais do ducto coletor, no nefrónio distal. O aumento da reabsorção de sódio a este nível – quer por atividade da aldosterona, quer por aumento da disponibilidade distal de sódio – causa um aumento da secreção de potássio no lúmen tubular. Dentro das causas de hipocaliemia por perdas renais, existem entidades se encontram mais associadas à PHP, tais como as doenças tubulares hereditárias, como a síndrome de Bartter e a síndrome de Gitelman, e as acidoses tubulares renais.

A síndrome de Gitelman é uma doença genética autossómica recessiva, causada por mutações de inativação no gene *SLC12A3*, localizado no cromossoma 16q, que codifica um cotransportador de sódio no túbulo contornado distal, thiazide-sensitive Na-Cl cotransporter, podendo esta inativação cursar com hipocaliemia, alcalose metabólica, hipomagnesémia, hipercalciúria e hiperreninémia. Geralmente é diagnosticada na adolescência / início da idade adulta, mas o fenótipo é altamente heterogéneo em termos de gravidade e manifestações clínica: na maioria das vezes, cursa com alterações iónicas ligeiras, porém, pode apresentar-se com distúrbios iónicos graves e apresentações floridas tais como a PHP.[34,35]

A síndrome de Gitelman adquirida é muito rara e praticamente apenas relatada em associação com doenças autoimunes, nomeadamente a síndrome de Sjögren. É caracterizada pela presença dos mesmos distúrbios iónicos e ácido-base, mas na ausência de mutações genéticas típicas associadas à síndrome de Gitelman hereditária. Apenas oito casos foram relatados em doentes com síndrome de Sjögren primária e em três desses doentes a apresentação ocorreu sob a forma de PHP.[36]

O envolvimento renal é uma manifestação frequente da síndrome de Sjögren e pode preceder o início dos sintomas *sicca*. Para além da síndrome de Gitelman adquirida, pode manifestar-se sob a forma de nefrite intersticial crónica, glomerulopatia, acidose tubular distal e diabetes insípida nefrogénica. Também a acidose tubular renal distal, em algumas casuísticas descrita em 25% dos doentes com síndrome de Sjögren, pode cursar com PHP.[36,37]

Existem ainda outras causas de PHP descritos na literatura, mais raras, envolvendo perdas renais de potássio, tais como a estenose unilateral da artéria renal[38] ou o consumo excessivo de diuréticos.[39]

Perdas gastrointestinais

Os casos de PHP associados a perdas gastrointestinais estão sobretudo associados a perdas crónicas, descritos na doença celíaca[40] e na diarreia causada por tumores neuroendócrinos com secreção aumentada de péptido intestinal vasoactivo.[41] Ainda assim, existem alguns casos de apresentação aguda por vómitos e diarreia exuberantes na gastroenterite infeciosa.[42]

Causas menos frequentes

Outras causas menos frequentes de PHP têm sido identificadas, nomeadamente:

Farmacológicas – As causas farmacológicas de PHP têm por base os mecanismos fisiopatológicos previamente descritos. A insulina e os agonistas dos recetores beta-adrenérgicos podem induzir PHP ao estimular a atividade da Na+/K+ ATPase e promover a entrada de potássio no meio intracelular.[43,44] Estão também descritos casos de PHP ao uso de corticosteróides, quer por ativação direta da Na+/K+ ATPase, quer por aumento da secreção de insulina, sobretudo em estados de tireotoxicose.[45,46] Na gravidez foram descritos episódios de PHP precipitada pela hiperinsulinemia na prova de tolerância oral a glucose ou pela administração de corticoterapia na maturação pulmonar.[47]

Tóxicas – podem ocorrer episódios de PHP associados a intoxicação por metais pesados, como o bário, presente por exemplo, em raticidas; que promove a ação da bomba Na+/K+ ATPase e reduz o efluxo de potássio.[4] O consumo de cocaína, um agonista adrenérgico de ação indireta, é outra causa conhecida.[48]

Infeciosas – a PHP pode ser uma manifestação clínica rara da infeção por dengue, quer por redistribuição do potássio intracelular, quer por alterações transitórias a nível tubular renal.[49] Outras infeções com casos descritos na literatura são a malária, a leptospirose e a Chikungunya.[50-52]

Mais recentemente foram também descritos casos de PHP em doentes com COVID-19. Pensa-se que o mecanismo subjacente poderá estar relacionado com a hiperactivação do sistema renina-angiotensina-aldosterona com subsequente aumento da excreção renal de potássio. No entanto são necessários estudos adicionais que corroborem esta teoria.[53,54]

Proposta de modelo esquemático da fisiopatologia da PHPS

Na fisiopatologia da PHPS, apesar de geralmente se encontrar presente um fator dominante, verifica-se uma contribuição multifatorial para um estado de hipocaliémia e consequente paralisia periódica. A Fig. 2 representa uma proposta de modelo esquemático da fisiopatologia da PHPS, representando os principais agentes

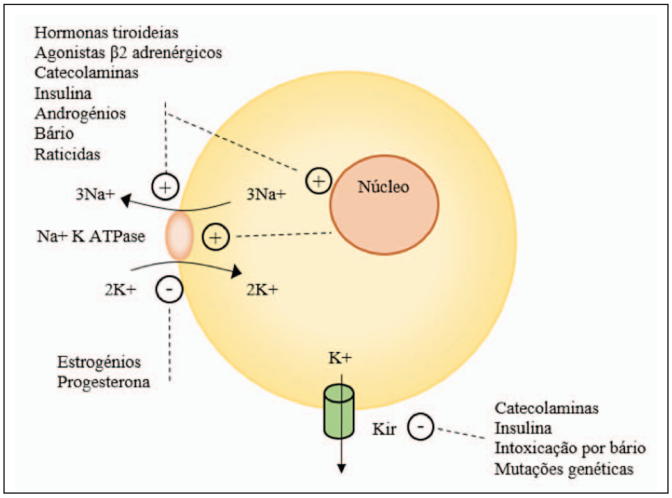


Figura 2. Mecanismos envolvidos na homeostase do potássio e fisiopatologia da paralisia hipocaliémica periódica.
Adaptado de: Iqbal QZ, *et al*. A Literature Review on Thyrotoxic Periodic Paralysis. Cureus. 2020; 12:e10108. doi: 10.7759/cureus.10108.[11]; Lin SH, *et al.* Mechanism of thyrotoxic periodic paralysis. J Am Soc Nephrol. 2012; 23:985–8. doi:10.1681/ASN.2012010046[12]

encontrados com capacidade de contribuir para um estado de PHP.

Conclusão

A PHP é incomum, mas deve ser considerada no diagnóstico diferencial da paralisia flácida aguda. Representa um grupo heterogéneo caracterizado por hipocaliemia e tetraparesia. A maioria dos casos são devidos a paralisia periódica familiar.

Na população adulta, o nível de suspeição para causas secundárias deve conduzir a uma história clínica detalhada e respetivos exames complementares. Na etiologia secundária, predominam os casos de PPT, embora a etiologia varie entre diferentes etnias e áreas geográficas. Apesar da investigação clínica crescente, alguns casos permanecem idiopáticos.

A base do tratamento na paralisia hipocaliémica periódica secundária é a reposição de potássio e o tratamento da causa subjacente que deve ser célere, tendo em conta o carácter potencialmente fatal desta patologia rara. A maioria da literatura de que dispomos provém de casos clínicos e casuísticas na população asiática. São necessários mais estudos para caracterizar a PHP na população caucasiana.

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HP, SB, MM: pesquisa de literatura, análise e interpretação dos dados; elaboração do artigo.
CN, JMA, SG, CV: revisão crítica do conteúdo nas várias versões e aprovação final.

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References / Referências

1. Fontaine B. Periodic paralysis. Adv Genet. 2008; 63:3-23. doi: 10.1016/S0065-2660(08)01001-8.
2. Fialho D, Griggs RC, Matthews E. Periodic paralysis. Handb Clin Neurol. 2018; 148:505-20. doi: 10.1016/B978-0-444-64076-5.00032-6.
3. Farooque U, Cheema AY, Kumar R., Saini G, Kataria S. Primary Periodic Paralyses: A Review of Etiologies and Their Pathogeneses. Cureus. 2020; 12: e10112. doi:10.7759/cureus.10112.
4. Ahlawat SK, Sachdev A. Classic diseases revisited: Hypokalaemic paralysis. Postgrad Med J. 1999; 75:193–7. doi.org/10.1136/pgmj.75.882.193(2005).
5. Chan A, Shinde R, Chow CC, Cockram CS, Swaminathan R. In vivo and in vitro sodium pump activity in subjects with thyrotoxic periodic paralysis. BMJ. 1991; 303:1096–9. doi.org/10.1136/bmj.303.6810.1096.
6. Nicoletti T, Modoni A, Silvestri G. Secondary hypokalemic periodic paralysis as a rare clinical presentation of Conn syndrome. Clinical Neurophysiology. 2018; 129:2505–6. doi.org/10.1016/j.clinph.2018.09.003.
7. Lin SH. Thyrotoxic Periodic Paralysis. Mayo Clinic Proc. 2005; 80:99–105. doi.org/10.4065/80.1.99.
8. Oliveira R, Ramalho Rocha F, Teodoro T, Oliveira Santos M. Acute non-traumatic tetraparesis – Differential diagnosis. J Clin Neurosci. 2021; 87:116–24. doi.org/10.1016/j.jocn.2021.02.024.
9. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. Adv Physiol Educ. 2016; 40:480–90. doi.org/10.1152/advan.00121.2016.
10. Iqbal QZ, Niazi M, Zia Z, Sattar SBA. A Literature Review on Thyrotoxic Periodic Paralysis. Cureus. 2020; 12:e10108. doi: 10.7759/cureus.10108.
11. Falhammar H, Thorén M, Calissendorff J. Thyrotoxic periodic paralysis: clinical and molecular aspects. Endocrine. 2013; 43, 274–284. doi:10.1007/s12020-012-9777-x.
12. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. J Am Soc Nephrol. 2012; 23:985–8. doi:10.1681/ASN.2012010046.
13. Puwanant A, Ruff RL. INa and IKir are reduced in Type 1 hypokalemic and thyrotoxic periodic paralysis. Muscle Nerve. 2010;42:315-27. doi: 10.1002/mus.21693.
14. Mount D. Causes of hypokalemia in adults. Uptodate. 2022. [Consultado a 29 Março 2022] Available from: https://www.uptodate.com/contents/causes-of-hypokalemia-in-adults.
15. Sardar Z, Waheed Kh AF, Javed MA, Akhtar F, Bokhari SR. Clinical and Etiological Spectrum of Hypokalemic Periodic Paralysis in a Tertiary Care Hospital in Pakistan. Cureus. 2019; 11: e3921. doi:10.7759/cureus.3921
16. Magsino CH Jr, Ryan AJ Jr. Thyrotoxic periodic paralysis. South Med J. 2000; 93:996–1003. PMID: 11147484.
17. Yokota N, Uchida T, Sasaki A, Kobayashi K, Kida O, Yamamoto Y, et al. Thyrotoxic Periodic Paralysis Complicated with Primary Aldosteronism. Japan J Med. 1991; 30:219-23. doi.org/10.2169/internalmedicine1962.30.219.
18. Hsieh MJ, Lyu RK, Chang WN, Chang KH, Chen CM, Chang HS, et al. Hypokalemic thyrotoxic periodic paralysis: clinical characteristics and predictors of recurrent paralytic attacks. Eur J Neurol. 2008; 15:559–64. doi.org/10.1111/j.1468-1331.2008.02132.x
19. Hannon MJ, Behan LA, Agha A. Thyrotoxic periodic paralysis due to excessive L-thyroxine replacement in a Caucasian man. Ann Clin Biochem. 2009; 46:423–5. doi.org/10.1258/acb.2009.009012.
20. Ryan DP, da Silva MR, Soong TW, Fontaine B, Donaldson MR, Kung AW, et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. Cell. 2010; 140:88. doi: 10.1016/j.cell.2009.12.024.
21. Cheng CJ, Lin SH, Lo YF, Yang SS, Hsu YJ, Cannon SC, Huang CL. Identification and functional characterization of Kir2.6 mutations associated with non-familial hypokalemic periodic paralysis. J Biol Chem. 2011; 286: 27425–35. doi: 10.1074/jbc.M111.249656.
22. Shih-Hua L. Thyrotoxic Periodic Paralysis. Mayo Clin Proc. 2005; 80:99-105. doi: 10.1016/S0025-6196(11)62965-0.
23. Manoukian MA, Foote JA, Crapo LM. Clinical and metabolic features of thyrotoxic periodic paralysis in 24 episodes. Arch Intern Med. 1999; 159:601-6. doi: 10.1001/archinte.159.6.601.
24. Lu KC, Hsu YJ, Chiu JS, Hsu YD, Lin SH. Effects of potassium supplementation on the recovery of thyrotoxic periodic paralysis. Am J Emerg Med. 2004; 22:544-7. doi: 10.1016/j.ajem.2004.09.016.
25. Galati SJ. Primary aldosteronism: Challenges in diagnosis and management. Endocrinol Metab Clin North Am. 2015;44:355–69. doi: 10.1016/j.ecl.2015.02.010.
26. Wrenn SM, Vaidya A, Lubitz CC. Primary aldosteronism. Gland Surg. 2020;9:14-24. doi:10.21037/gs.2019.10.23.
27. Ma JT, Wang C, Lam KS, Yeung RT, Chan FL, Boey J, et al. Fifty cases of primary hyperaldosteronism in Hong Kong Chinese with a high frequency of periodic paralysis. Evaluation of techniques for tumour localisation. Q J Med. 1986;61:1021-37.
28. Balhana S, Pina H, Machete M, Aragues JM, Noronha C. Conn's syndrome: an unusual cause of periodic paralysis. Cureus. 2022; 14: e24880. doi:10.7759/cureus.24880.
29. Elson MJ, Wang VL, Sharma J. Management of Conn's Syndrome Associated with Hypokalemic Nonperiodic Paralysis. Am Surg. 2020; 1;86:e33-e34.
30. Hsiao YH, Fang YW, Leu JG, Tsai MH. Hypokalemic Paralysis Complicated by Concurrent Hyperthyroidism and Hyperaldosternoism: A Case Report. Am J Case Rep. 2017; 18:12–6. doi.org/10.12659/AJCR.901793.
31. Armanini D, Calò L, Semplicini A. Pseudohyperaldosteronism:

pathogenetic mechanisms. Crit Rev Clin Lab Sci. 2003;40:295-335. doi: 10.1080/713609355.

32. Lanzi R, Previtali SC, Sansone V, Scavini M, Fortunato M, Gatti E, et al. Hypokalemic periodic paralysis in a patient with acquired growth hormone deficiency. J Endocrinol Invest. 2007; 30:341–5. doi. org/10.1007/BF03346302.
33. Soonthornpun S, Setasuban W, Thamprasit A. Insulin resistance in subjects with a history of thyrotoxic periodic paralysis (TPP). Clin Endocrinol. 2009;70:794-7. doi: 10.1111/j.1365-2265.2008.03395.x.
34. Gandhi K, Prasad D, Malhotra V, Agrawal D. Gitelman′s syndrome presenting with hypocalcemic tetany and hypokalemic periodic paralysis. Saudi J Kidney Dis Transpl. 2016; 27:1026. doi.org/10.4103/1319-2442.190881.
35. Sinaga F, Naibaho RM, Sibuea WH. Gitelman syndrome: an important cause of severe hypokalemia and periodic paralysis. World J Nephrol Urol. 2016; 5:40–7. doi.org/10.14740/wjnu270e.
36. Ranaweerage R, Perera S, Gunapala A. Hypokalaemic paralysis and metabolic alkalosis in a patient with Sjögren syndrome: a case report and literature review. BMC Nephrol. 2021; 22:159. https://doi.org/10.1186/s12882-021-02371-5.
37. Yılmaz H, Kaya M, Özbek M, Üreten K, Safa Yıldırım İ. Hypokalemic periodic paralysis in Sjogren's syndrome secondary to distal renal tubular acidosis. Rheumatol Int. 2013; 33:1879–82. doi.org/10.1007/s00296-011-2322-z.
38. Singh PK, Rajput R, Banerjee S, Garg K. Unilateral renal artery stenosis presenting as acute flaccid paralysis: a rare presentation. BMJ Case Rep. 2018; bcr-2018-225889. doi.org/10.1136/bcr-2018-225889.
39. Pfisterer N, Stöllberger C, Finsterer J. Severe Acquired Hypokalemic Paralysis in a Bodybuilder After Self-Medication with Triamterene/Hydrochlorothiazide. Clin J Sport Med. 2020; 30:e172–e174. doi. org/10.1097/JSM.0000000000000763.
40. Gupta T, Mandot A, Desai D, Abraham P, Joshi A. Celiac crisis with hypokalemic paralysis in a young lady. Indian J Gastroenterol. 2016; 25:259-60.
41. Ramirez S, Lytle M, Togores E, Parellada J, Carlan SJ, Madruga M, et al. Successful Treatment of Hypokalemic Rhabdomyolysis Caused by a Pancreatic VIPoma: A Case Report. Am J Case Rep. 2019; 20: 1723–7. doi.org/10.12659/AJCR.918213.
42. Orman RA, Lewis JB Jr. Flaccid quadriparesis associated with Yersinia enterocolitis-induced hypokalemia. Arch Intern Med. 1989; 149:1193-4.
43. Ruff RL. Insulin acts in hypokalemic periodic paralysis by reducing inward rectifier K current. Neurology. 1999; 53:1556. doi.org/10.1212/WNL.53.7.1556.
44. Tucker C, Villanueva L. Acute hypokalemic periodic paralysis possibly precipitated by albuterol. Am J Health-Syst Pharm. 2013; 70:1588–91. doi.org/10.2146/ajhp130086.
45. Wongraoprasert S, Buranasupkajorn P, Sridama V, Snabboon T. Thyrotoxic Periodic Paralysis Induced by Pulse Methylprednisolone. Intern Med. 2017; 46:1431–4. doi.org/10.2169/internalmedicine.46.0044.
46. Tigas S, Papachilleos P, Ligkros N, Andrikoula M, Tsatsoulis A. Hypokalemic paralysis following administration of intravenous methylprednisolone in a patient with Graves' thyrotoxicosis and ophthalmopathy. Hormones. 2011; 10:313–6. doi.org/10.14310/horm.2002.1323.
47. Kulkarni M. Hypokalemic paraplegia in pregnancy. J Clin Diagn Res. 2014; 8:OD03-4. doi.org/10.7860/JCDR/2014/8793.4433.
48. Lajara-Nanson WA. Cocaine induced hypokalaemic periodic paralysis. J Neurol Neurosurg Psychiatry. 2002; 73:92. doi.org/10.1136/jnnp.73.1.92.
49. Roy A, Tripathi AK, Verma SP, Reddy H, Jain N. Acute hypokalaemic quadriparesis in dengue fever. Case Rep. 2011; bcr1120103514. doi. org/10.1136/bcr.11.2010.3514.
50. Sinha S, Mukherji A, Chandrakar S. Hypokalaemic paralysis in an adult case of Plasmodium vivax malaria. Malaria Journal. 2013; 12:111. doi. org/10.1186/1475-2875-12-111.
51. Baburaj P, Varma SS, Harikrishnan BL. Hypokalemic paralysis in leptospirosis. J Assoc Physicians India. 2012; 60:53-4.
52. Rampal, Sharda M, Meena H. Hypokalemic paralysis following Chikungunya fever. J Assoc Physicians India. 2007; 55:598.
53. Kaushik A, Garg A, Singh BM, Agarwal AK, Wani SN. Hypokalaemic paralysis associated with COVID-19 Infection. J Assoc Physicians India. 2021; 69:78-9.
54. Chen D, Li X, Song Q, Hu C, Su F, Dai J, et al. Assessment of Hypokalemia and Clinical Characteristics in Patients With Coronavirus Disease 2019 in Wenzhou, China. JAMA Network Open. 2020; 3:e2011122. doi. org/10.1001/jamanetworkopen.2020.11122.

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Artigo Revisão

Carcinoid Syndrome: A Review

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A B S T R A C T

Carcinoid syndrome (CS) is a debilitating disease caused by the production of a variety of biologically active substances by functional neuroendocrine neoplasms (NENs). While the reported frequency of CS among NEN patients has been inconsistent, the negative impact on patient quality of life is clearly established.
The cardinal presenting features of CS are flushing, diarrhoea, abdominal pain and valvular heart disease; other signs and symptoms can include wheezing, telangiectasias, pellagra, and the complications of mesenteric fibrosis, including bowel obstruction and ischemia. These symptoms are mediated by the release of serotonin, histamine, kallikrein, prostaglandins and tachykinins.
There have been advances in many aspects of the carcinoid-syndrome all of which are reviewed in this article, including new methods to establish diagnosis, an increased understanding of natural history and pathogenesis and important new approaches to its treatment.

Palavras-chave:
Síndrome do Carcinoide Maligno/diangóstico;
Síndrome do Carcinoide Maligno/fisiopatologia;
Síndrome do Carcinoide Maligno/tratamento farmacológico;
Tumores Neuroendócrinos/complicações.

Síndrome Carcinóide: Revisão

R E S U M O

A síndrome carcinóide (SC) é uma doença debilitante causada pela produção de múltiplas substâncias biológicas ativas por neoplasias neuroendócrinas (NENs). Apesar da variabilidade na frequência reportada, o impacto negativo na qualidade de vida dos pacientes com NENs está bem estabelecido.
A apresentação clássica da SC inclui o *flushing*, a diarreia, a dor abdominal e a doença valvular cardíaca; outros sinais e sintomas incluem o broncoespasmo, telangiectasias, pelagra e as complicações da fibrose mesentérica como obstrução e isquemia intestinal. Estes sintomas são mediados pela libertação de serotonina, histamina, calicreína, prostaglandinas e taquicininas.
A síndrome carcinóide tem sido alvo de vários avanços, incluindo novos métodos de diagnóstico, um aperfeiçoamento na compreensão da sua história natural e patogénese, e novas abordagens terapêuticas, que serão abordados neste artigo.

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1. Introduction

Carcinoid syndrome (CS) is a debilitating disease caused by the production of a variety of biologically active substances by functional neuroendocrine neoplasms (NEN).[1] The classical example of a hormonal syndrome, CS was first described in 1931.[2] Recently, the frequency of CS was assessed in a Surveillance, Epidemiology, and End Results (SEER) database in the USA; the authors have reported an increasing incidence of carcinoid syndrome between 2000 and 2011 and, among the 9512 patients diagnosed with NEN over this period, symptoms of CS were reported in 18.8%.[3] While the reported frequency of CS among NEN patients has been inconsistent, the negative impact on patient quality of life(QoL) is clearly established.[4–6]

2. Pathophysiology

Neuroendocrine neoplasms may secrete numerous active substances that are potential mediators of the clinical features of CS; the most prominent being 5-hydroxytryptamine (5-HT, serotonin), commonly used to assess for the presence of CS by determining the serotonin-metabolite, 5-hydroxy-indole acetic acid (5-HIAA), in the urine.[7] Due to the absence of the aromatic amino acid decarboxylase, that converts 5-hydroxytryptophan (5-HTP) to 5-HT, foregut NEN secrete 5-HTP instead of 5-HT (see atypical carcinoid syndrome).[7] Other co-secreted peptide hormones and amines include tachykinins (substance P and neurokinin A), bradykinins, histamine and prostaglandins.[7]

Serotonin is considered the main mediator of diarrhoea in CS, due to its effects on gut motility and secretion,[8–11] and a main driver of fibrotic complications such as retroperitoneal, mesenteric and cardiac valvular fibrosis in carcinoid heart disease.[10–14] On the other hand, bronchial constriction is predominantly mediated by tachykinins and bradykinins that cause constriction of smooth muscle in the respiratory tract and local oedema in the airways.[10,15] Although the cutaneous flushing pathophysiology is not well established yet, several vasodilators, such as tachykinins, bradykinins, prostaglandins, and histamine are thought to be involved.[10,15,16]

Carcinoid syndrome occurs when sufficient amount of tumour-released bioactive products reaches the systemic circulation, escaping the first pass inactivation in the liver.[1,10] Carcinoid syndrome is thus predominantly encountered in patients with midgut NENs with liver metastases, in which these bioactive products escape inactivation in the liver.[10] Ovarian NENs and large retroperitoneal metastases from midgut NENs are associated with CS in the absence of liver metastases as bioactive amines are released directly into the systemic circulation, bypassing hepatic inactivation.[10] The inactivation of the bioactive tumour products also occurs in the pulmonary circulation; the predominance of right-sided plaque-like thickenings of endocardium, valves, atria and ventricles in carcinoid heart disease supports this mechanism and differential exposure.[7,10,12] The exception, with both left and right-sided heart-valves involvement, is seen in bronchial NENs or in right-to-left shunt.[7,10,12]

3. Clinical features

The cardinal presenting features of the CS are flushing, secretory diarrhoea, abdominal pain and valvular heart disease[14]; nevertheless, a typical patient with CS may also present with telangiectasia, valvular heart disease, intermittent bronchial wheezing, and pellagra.[7,17]

3.1 Flushing

Flushing is a subjective sensation of warmth that is accompanied by reddening of the skin anywhere on the body but favours the face, neck, and upper torso.[18] Flushing in CS may occur spontaneously or be triggered by stress (physical and emotional), alcohol, drugs (pentagastrin, catecholamines, dopamine, isoproterenol), exercise or tyramine-containing-foods like chocolate, bananas, cheese, red wine or walnuts.[14,16,19] Four types of flushing are distinguished: erythematous, violaceous, prolonged and bright red.[19]

The first type is the sudden, short-lived (1 to 5 minutes) and diffuse erythematous flush, usually affecting the face, neck, and upper chest; it is associated to early-stage midgut NENs.[14,17]

The second type is the violaceous flush; it affects the same area of the body and has approximately the same time course as the erythematous flush. Additionally, patients may also have facial telangiectasias and may not report the flushing as they have become accustomed.[19] This kind of flush occurs during the later stages of midgut NENs.[19]

The third type is prolonged flushing, lasting from a couple of hours to several days; it may involve the whole body and it is sometimes associated with profuse lacrimation, swelling of the salivary gland, hypotension, and facial oedema; this type of flushing is usually associated with malignant bronchial NENs and is thought to be 5-HTP and/or histamine-induced.[17,19]

The fourth type is a bright red, patchy flush seen in patients with chronic atrophic gastritis and gastric enterochromaffin cell hyperplasia; these symptoms are associated with an increased release of histamine.[17,19]

The differential diagnosis of flushing includes both physiologic (such as menopause) and pathologic causes from non-neuroendocrine disorders (POEMS syndrome, central hypogonadism, orthostatic hypotension, panic attacks) to other neuroendocrine entities (medullary thyroid carcinoma, pheochromocytoma and paraganglioma, endogenous Cushing's syndrome).[16,19]

3.2 Diarrhoea

The diarrhoea is typically secretory and intermittent, often associated with abdominal cramping which may result from mesenteric fibrosis.[17,19] Malabsorption features can develop from intestinal resections, lymphangiectasia, secondary to mesenteric fibrosis, from bacterial overgrowth, intestinal blockage by the primary tumour or rapid intestinal transit. Additionally, increased secretion by the small bowel associated with accelerated transit can overwhelm the normal storage and absorptive capacity of proximal colon.[17,19]

In a study of patients with CS, transit time in the small bowel and colon was significantly decreased when compared to normal subjects; the volume of the ascending colon was smaller, and the postprandial colonic tone increased.[20] Overall, although initially a secretory one, diarrhoea can develop malabsorption features and associate alterations in gut motor function.[19,20] Nevertheless, determining the underlying cause of diarrhoea can be challenging as patients with NENs may experience uncontrolled diarrhoea due to surgical complications or treatment with somatostatin analogues; pancreatic exocrine insufficiency, inflammatory bowel disease, irritable bowel syndrome, lactose intolerance or celiac disease are other etiologies to consider.[21]

3.3 Carcinoid heart disease (Hedinger's syndrome)

Carcinoid heart disease (CHD) is a severe complication of CS characterized by the development of plaque-like fibrous endocardial

thickening that affects primarily the right-sided valves.[12,17,19] It is associated with increased morbidity and mortality, leading to progressive dysfunction of the cardiac valves and ultimately to congestive heart failure.[12] Echocardiography can demonstrate lesions in about 60%-80% of CS patients although it is clinically significant in a much smaller percentage.[12,17,19] Prevalence of CHD has decreased to approximately 20%, probably due to earlier CS diagnosis and initiation of antitumour treatment such as somatostatin analogues.[12,17,19,,22]

There is often an asymptomatic period; in symptomatic patients, dyspnoea and fatigue are the most encountered symptoms.[12] Patients with ≥3 episodes of flushing per day and those who have significantly higher levels of urinary 5-HIAA (see diagnosis) are at increased risk of developing CHD; this latter biomarker has been shown to be an independent predictor for the development and progression of CHD.[12,17,19,22–24]

3.4 Other clinical features

Bronchial constriction with wheezing may be present, particularly during a carcinoid crisis.[17,19] Fibrotic complications other than CHD may occur, such as intra-abdominal fibrosis (that can lead to intestinal adhesions and bowel obstruction), retroperitoneal fibrosis (that may result in obstruction of the ureter with kidney function impairment), occlusion of the mesenteric arteries and veins, Peyronie's disease and carcinoid arthropathy.[17,19] Other rare features of CS result from diversion of dietary tryptophan for synthesis of serotonin which may develop pellagra (skin rashes, glossitis, stomatitis, dementia/mental confusion) and reduced protein synthesis with hypoalbuminemia and myopathy.[17,19]

3.5 Carcinoid crisis

Carcinoid crisis is a severe and potentially life-threatening exacerbation of hormonal symptoms of the CS, due to the release of large amounts of amines in the circulation.[17] Hypotension, rarely hypertension, tachycardia, arrhythmias, hyperthermia, bronchoconstriction, severe flushing and central nervous system dysfunction dominate the clinical presentation.[17,19,25] Carcinoid crisis can occur spontaneously or be precipitated by anaesthesia, infection, chemotherapy or interventional procedures (surgery, embolization procedures, peptide receptor radionuclide therapy).[17,19,25,26] Concerning anaesthesia, drugs that stimulate the sympathetic nervous system or cause histamine release, such as morphine and d-tubocurarine should be avoided; propofol has a more profound effect in supressing catecholamine release and may the best agent in patients with CS as long as hypotension is avoided.[25] Intravenous octreotide might be used in combination with volume expanders to correct hypotension; the latter can also have a role in the treatment of bronchospasm as β-receptor agonist and theophylline may precipitate mediator release; corticosteroids (dexamethasone) may also be used.[25]

The presence of a high tumour load, CHD, high urinary 5-HIAA values or high chromogranin A levels are risk factors for the development of carcinoid crisis.[25] Peri-operative carcinoid crisis prophylaxis with somatostatin analogues is advised (see treatment).[25]

3.6 Atypical carcinoid syndrome

An atypical carcinoid syndrome may be encountered in patients with tumours originating from the foregut including mostly the lung, but also the stomach and duodenum.[19,25] Patients with the atypical carcinoid syndrome have a decarboxylation deficit and therefore only seldom have excess urinary excretion of the serotonin metabolite 5-HIAA.[19,25] The syndrome consists of patchy, intensely red flush, sweating, itching, sometimes also cutaneous oedema, bronchoconstriction, salivary gland swelling, lacrimation, and cardiovascular instability mainly manifested as hypotension and it is due to the release of both histamine and serotonin.[19,25] Like typical carcinoid syndrome patients, in the presence of an atypical carcinoid syndrome, the patients should be treated with somatostatin analogues and a combination of histamine-1(H1) and histamine-2(H2) receptor blockers as prophylaxis treatment of carcinoid crisis before, during and after high-risk procedures.[25]

3.7 Refractory carcinoid syndrome

Refractory carcinoid syndrome (RCS) is defined by recurring or persisting CS symptoms and increasing or persistently high urinary 5-HIAA levels despite the use of maximum label doses of SSA.[27] RCS may be divided into either non-aggressive or aggressive, based on symptoms burden (<4 or ≥ bowel movements per day, and/or < or ≥ 5 flushing episodes per day, respectively) together with disease stability (stable or progressive), hepatic burden (< or ≥ 50% liver involvement) and/or the presence of carcinoid heart disease.[27]

4. Diagnosis

The presence of CS is considered when a patient has suggestive symptoms.[7,19] The most frequent initial diagnostic method is assessment of 5-HIAA levels.[7]

4.1 Biochemical diagnosis

The preferred initial diagnostic test for CS is to measure 24-hour urinary excretion of 5-HIAA; various foods and drugs (Table 1) can

Table 1. Factors that interfere with urinary 5-HIAA measurement [adapted from[19]]

Factors that produce false-positive results	
Foods	Drugs
Avocado	Acetaminophen
Banana	Acetanilide
Chocolate	Caffeine
Coffee	Fluorouracil
Eggplant	Guaifenesin
Pecan	L-Dopa
Pineapple	Melphalan
Plum	Mephenesin
Tea	Metamphetamine
Walnuts	Methocarbamol
	Methydergide maleate
	Phenmetrazine
	Reserpine
	Salicylates
Factors that produce false-negative results	
Foods	Drugs
None	Corticotropin
	p-Chlorophenylalanine
	Chlorpromazine
	Heparin
	Isoniazid
	Methenamine mandelate
	Methyldopa
	Monoamine oxidase inhibitors
	Phenothiazine
	Promethazine

interfere with the measurement and patients should avoid them for two to three days prior to urine collection.[7,19,28] Normal rate of urinary 5-HIAA excretion is <10 mg/day; elevated levels are usually found but foregut NENs tend to produce an atypical CS with normal or only slightly elevated 5-HIAA.[19] Measurement of 5-HIAA levels in all patients with small intestinal NENs is recommended because few patients may display high 5-HIAA levels in the absence of a clinical syndrome.[29]

Recently, a serum 5-HIAA measurement method has been developed with close correlation with urinary 5-HIAA; the absence of food interference and the ability to assess 5-HIAA levels with a single determination are the main advantages.[7,30,31]

4.2 Diagnosis of carcinoid heart disease

Transthoracic echocardiography is the gold-standard for the diagnosis and monitoring of carcinoid heart disease and several echocardiographic scoring systems were developed; cardiac magnetic resonance imaging (MRI) may have a complementary role in the diagnosis.[12,32] N-terminal pro-B type natriuretic peptide (NT-proBNP) is the most appropriate marker with both diagnostic and prognostic value for heart diseases; in patients with CS the cut-off value in CHD screening is 260 pg/mL((31 pmol/L).[32] Another useful marker in the assessment of CHD is 5-HIAA; a 24-hour urinary 5-HIAA >300 mmol/L helps identify subjects with increased risk of CHD development.[32]

5. Treatment

The treatment of choice for a patient who has a localized NEN is usually surgery with curative intent; systemic treatment options to control tumour growth and hormone hypersecretion and to improve patient's quality of life are used in metastatic NEN.[27]

5.1 Nutrition, lifestyle, and symptomatic treatment

Regular screening of nutritional status is required.[33] Tryptophan is the common precursor of serotonin and niacin (vitamin B3); in CS, as most niacin is metabolized to serotonin, niacin deficiency is common and can result in pellagra.[34] Supplementation with high-doses of niacin (50-500 mg/day) or niacin-enriched food may be required.[34] Additionally, deficiencies of fat-soluble vitamins, which may occasionally follow treatment with somatostatin analogues, should be sought and supplemented.[35]

For flushing, lifestyle adjustments include alcohol eviction as well as avoiding spicy foods and strenuous exercise.[33] Loperamide (doses up to 16 mg daily) can be used in refractory cases of diarrhoea.[33]

5.2 Pharmacologic treatment

Somatostatin analogues (SSAs)

Somatostatin is a peptide hormone that inhibits the secretion of a broad range of hormones by binding to somatostatin receptors which are expressed on the majority of NENs.[36] Somatostatin analogues targeting predominantly somatostatin receptor subtype 2, octreotide and lanreotide, are the standard initial treatment for CS for its anti-secretory and antiproliferative effects in NEN patients.[1] In a recent meta-analysis of studies with SSA in CS patients, octreotide induced a response of overall symptoms in 66%, of diarrhoea in 65% and of flushes in 72% of subjects; while lanreotide experienced similar responses rates of 65%, 65% and 69%, respectively.[1] Overall, control of the most relevant CS symptoms with doses of octreotide long acting-release (LAR) 20-30 mg or lanreotide autogel 90 to 120 mg every 4 weeks was obtained in 66%-70% of patients.[1] Biochemical response of 5-HIAA levels occurred in 45%-46% of CS patients.[1]

Despite the clear efficacy of SSAs, loss of response can occur after prolonged use. Downregulation of somatostatin receptors on tumour cell surface has been hypothesized to underlie tachyphylaxis.[1] Escalation of dose or frequency (to 21 days) of a SSA may be necessary for patients with refractory symptoms; these strategies result in a reduction of diarrhoea and flushes in 72% and 84% of the patients, respectively. However, 5-HIAA reduction was achieved in only 29%.[1] An alternative strategy, switching either octreotide or lanreotide to pasireotide, a SSA that targets somatostatin receptor subtypes 1-3 and 5, led to symptomatic response in 27% of patients.[37] However, a randomized phase III study of pasireotide LAR versus high-dose (40 mg) octreotide LAR in patients with advanced gastroenteropancreatic NENs failed to show superiority of pasireotide LAR in comparison with first-generation SSAs at maximum approved doses.[38] SSA treatment was associated with higher health-related quality of life (HR-QoL).[39,40]

Telotristat ethyl

Telotristat ethyl is a serotonin synthesis inhibitor, acting by inhibiting tryptophan hydroxylase, the rate-limiting enzyme in the production of serotonin from tryptophan.[10] On the TELESTAR trial, a three-arm study evaluating two doses of oral telotristat ethyl (250 and 500 mg, each taken three times daily) against placebo, conducted in patients with CS with uncontrolled diarrhoea (≥ 4 bowel movements daily) treated with SSA, the drug was associated with a significant reduction in bowel movement frequency and 5-HIAA levels.[41] Long-term improvement in HR-QoL was also reported.[42–44] The drug was well tolerated and is approved in combination with a SSA for the treatment of adults with CS-associated diarrhoea inadequately controlled with SSA monotherapy; the recommended dose is 250 mg three times daily.[41]

Interferon alpha

Interferon-α (IFN-α) exerts a direct effect on tumour cells by blocking cell division and reducing angiogenesis.[36] Additionally, IFN-α produces upregulation of somatostatin receptors, suggesting a synergistic effect.[45]

The recommended dose of INF-α is 3-9MU subcutaneously every other day; slow-release formulation is given subcutaneously once a week (80-100 mg).[46] In several single-arm prospective series, the reported response rates of INF monotherapy varied between 0%-90% and 50%-80% for clinical and biochemical control, respectively.[1] Patients with CS who have not responded to octreotide or IFN-α alone may be given a combination of both agents; such combinations have generated symptomatic control in 70% of patients and stabilization of tumour growth in 40% to 50% of patients.[19] Low tolerability of the drug due do its side effects (flu-like symptoms, chronic fatigue, liver and bone marrow toxicity, autoimmune reactions) limits its use to few experienced centers.[19]

Liver-directed therapies

Liver-directed therapies have been reported to be effective in controlling CS symptoms in SSAs resistant patients with disease limited to the liver; these include radiofrequency ablation, trans-

arterial chemoembolization/trans-arterial embolization, radioembolization or selective internal radiation therapy with 90y yttrium-labeled microspheres and hepatic-segment resection.[1]

Data on outcomes of liver-directed therapies is scarce; in most of the studies clinical response is described without further quantification, but overall reported clinical and biochemical response rates are high.[1] Most of the studies concerned treatments with embolization; when all embolization techniques were combined, response rates are 82% and 63% for overall symptoms and 5-HIAA levels, respectively.[1] The efficacy does not appear to be influenced by previous use of SSAs.[1]

Peptide receptor radionuclide therapy (PRRT)

The NETTER-1 study, conducted on patients with progressive metastatic midgut NENs to receive ^{177}Lu-DOTATE plus octreotide 30 mg LAR every four weeks vs high-dose octreotide (60 mg every four weeks), demonstrated improvement in clinically relevant symptoms such as diarrhoea and health-related quality of life with no significant change found on flushing.[47,49]

PRRT is usually well-tolerated with self-limiting acute side effects of nausea and vomiting; the potential exacerbation of hormonal syndromes leading to carcinoid crisis during/after PRRT although rare must be acknowledged.[49] The most serious long-term toxicity associated with PRRT is irreversible myelotoxicity and therapy-related myeloid neoplasms.[50]

Everolimus

A mechanistic target of rapamycin (mTOR) inhibitor, everolimus, proved its effectiveness in progression-free survival in non-functional lung or gastrointestinal NENs (RADIANT-4).[51] In another trial in patients with carcinoid syndrome (RADIANT-2), the combination of octreotide LAR 30 mg q28d with everolimus 10 mg daily was associated with a slight but significant improvement in 5-HIAA (61% *vs* 54% in octreotide LAR monotherapy), although no difference in the overall survival was noted and symptom control was not assessed.[52] Of note, everolimus side-effects, which include diarrhoea, may be challenging in CS patients.[52]

5.3 Treatment and prophylaxis of carcinoid crisis

Patients with CS are at risk of developing a carcinoid crisis during high-risk procedures (see above). Periprocedure prophylactic treatment of choice is intravenous octreotide at a starting dose of 50-100 µg/h with dose escalation until symptom control is obtained (mean dose of 100-200 µg/h).[25] Most experts initiate treatment at least 12 hours before the procedure and continue at least 48 hours after, as late-onset events have been described.[25] Patients pre-treated with SSAs may require even higher doses of intravenous octreotide.[25]

Patients with atypical carcinoid syndrome should be treated with prophylactic octreotide but may require higher doses (100-200 µg/h) and sometimes saline infusion. Combination treatment with H1 receptor blockers (loratadine), H2 blockers (ranitidine) and dexamethasone is recommended in severe cases to further block histamine release.[25]

Concerning anaesthesia, drugs that stimulate the sympathetic nervous symptoms or cause histamine release such as morphine and d-tubocurarine should be avoided; for anaesthesia induction, propofol may be the best agent as it has a more profound effect in supressing catecholamines release.[25] Only nondepolarizing neuromuscular blockers that do not cause histamine release should be used, vecuronium and rocuronium can be safely used. During maintenance of anaesthesia, attention should be paid to avoid right ventricular overload and strain to prevent right ventricular failure.[25] Hypotension is the most common problem during anaesthesia, and, in this case, sympathomimetic drugs should be avoided as they may worsen hypotension by triggering peptides release.[25] Hypotension tends to occur during manipulation of large bulky metastases; procedure should be stopped until hemodynamic control is restored and intravenous octreotide in association with volume expanders can be used.[25]

5.4 Treatment of carcinoid heart disease

The main challenge in CHD management rises from the necessity to simultaneously address the tumour burden (and 5-HT secretion), the CS symptoms, and the heart failure.

Antiproliferative and antisecretory therapy

Considering the crucial role of 5-HT in the cascade of events leading to the development of CHD, it is pivotal to control serotonin production from the tumour.[12]

Considering medical therapy, long-acting SSAs, octreotide and lanreotide (with association of telotristat ethyl if needed), have shown substantial reductions in serotonin production and antiproliferative effect (see above).[29]

Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE is an effective antiproliferative therapy in progressive disease refractory to first line SSAs; a particular concern with this therapy is volume overload in patients with heart failure due to the nephroprotective amino acid infusion as part of the PRRT protocol.[29] A prolonged infusion might be considered[53]; a recent report of nine CHD patients treated with PRRT showed no acute cardiac complications in association with PRRT.[54] However, patients with uncontrolled congestive heart failure [New York Heart Association (NYHA) class II-IV were not eligible for treatment with ^{177}Lu-DOTATTE treatment in NETTER-1 study.[48] Current ENETS guidelines consider severe cardiac impairment (NYHA class III or IV) an absolute contraindication.[55]

Non-cardiac interventions

Transcatheter arterial embolization (TAE) is an efficient method in decreasing tumour burden and hormone levels in individuals with substantial metastases in the liver.[29] However, it must be used with caution in patients with severe CHD and right ventricular dysfunction and/or high hepatic tumour burden due to potential adverse effects such as bleeding or liver failure.[29] It is recommended that TAE should be exploited in the early disease stages before cardiac insufficiency occurs and should be used with caution (embolization procedures can be staged, and different liver segments may be embolized in repetitive small sessions) when carcinoid heart disease is present.[29] Complete portal vein occlusion, poor performance status and hepatic insufficiency are considered relative contraindications.[29]

Surgical hepatic debulking decreases CHD progression and improves prognosis[58]; similar to TAE, debulking surgery should be performed with caution and its recommended for patients with advanced valve disease after heart valve replacement.[29]

Pharmacotherapy for heart failure

Medical management consists of relieving symptoms of right-sided heart failure with a combination of loop and thiazide diuretic agents, as well as aldosterone antagonist therapy.[29] However, these measures should be used judiciously, as depletion of intravascular volume can further reduce cardiac output, leading to fatigue and breathlessness.[57] Other treatments, including digoxin, vasodilators, and angiotensin-converting enzyme inhibitors, can be considered, but they have no proven efficacy in this population.[29,57]

Heart valve replacement

Heart valve replacement is the most effective treatment option for advanced carcinoid heart disease.[58] The optimal timing of surgery in relation to the severity of valve dysfunction and symptoms has not been identified; a recommended indication for valve replacement is right ventricular dysfunction (symptomatic or evidence in echocardiography) with at least 12 months of anticipated post-operative survival from their NEN.[29] A trend towards earlier intervention, including patients with metastatic NENs prior to any primary-tumour debulking surgery or liver-directed therapies, has been observed.[59,60] The choice of valve prosthesis should be individually tailored based on the patient's bleeding risk and possible future therapeutic interventions. Biological valve prostheses are the preferred option.[29] Prophylactic treatment for carcinoid crisis must be implemented in the peri-procedure period.[29]

6. Conclusion

In the last years there have been many advances in the management of NENs and its functional syndromes such as the more frequent, carcinoid syndrome. There is a strengthened awareness of its pathogenesis, its epidemiology and increasing frequency; new methods to establish its diagnosis and new approaches to its treatment, namely for patients with carcinoid syndrome refractory to somatostatin analogues. Carcinoid heart disease, a significant cause of morbidity and mortality in patients with carcinoid syndrome, has seen new non-surgical therapeutic advances with the potential to prevent its development or to slow its progression which has significantly improved the prognosis of these individuals.

The presence of the endocrinologist in the multidisciplinary care team is essential for the management of these neoplasms, as many functioning tumours may be underdiagnosed in non-specialized centers.

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References / Referências

1. Hofland J, Herrera-Martínez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. Endocr Relat Cancer. 2019;26:R145-R156. doi:10.1530/ERC-18-0495
2. Scholte A. Ein fall von angioma teleangiectaticum cutis mit chronischer endocarditis und malignem dünndarmcarcinoid. Beitrage Pathol Anat. 1931;86:440-443.
3. Halperin DM, Shen C, Dasari A, Xu Y, Chu Y, Zhou S, Shih YT, Yao JC. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol. 2017;18:525-34. doi: 10.1016/S1470-2045(17)30110-9.
4. Fröjd C, Larsson G, Lampic C, von Essen L. Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study. Health Qual Life Outcomes. 2007;5:1-9. doi:10.1186/1477-7525-5-18/TABLES/5
5. Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas. 2012;41:461-6. doi:10.1097/MPA.0B013E3182328045
6. Pearman TP, Beaumont JL, Cella D, Neary MP, Yao J. Health-related quality of life in patients with neuroendocrine tumors: an investigation of treatment type, disease status, and symptom burden. Support Care Cancer. 2016;24:3695-703. doi:10.1007/S00520-016-3189-Z
7. Ito T, Lee L, Jensenc RT. Carcinoid-syndrome: recent advances, current status and controversies. Curr Opin Endocrinol Diabetes Obes. 2018;25:22. doi:10.1097/MED.0000000000000376
8. Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes. 2013;20:14-21. doi:10.1097/MED.0B013E32835BC703
9. Jackson LN, Chen LA, Larson SD, Silva SR, Rychahou PG, Boor PJ, et al. Development and characterization of a novel in vivo model of carcinoid syndrome. Clin Cancer Res. 2009;15:2747-55. doi: 10.1158/1078-0432.CCR-08-2346.
10. Fanciulli G, Ruggeri RM, Grossrubatscher E, Calzo FL, Wood TD, Faggiano A, et al. Serotonin pathway in carcinoid syndrome: Clinical, diagnostic, prognostic and therapeutic implications. Rev Endocr Metab Disord. 2020;21:599-612. doi: 10.1007/s11154-020-09547-8.
11. Gustafsson BI, Tømmerås K, Nordrum I, et al. Long-term serotonin administration induces heart valve disease in rats. Circulation. 2005;111:1517-22. doi:10.1161/01.CIR.0000159356.42064.48
12. Koffas A, Toumpanakis C. Managing carcinoid heart disease in patients with neuroendocrine tumors. Ann Endocrinol. 2021;82:187-192. doi:10.1016/J.ANDO.2020.12.007
13. Laskaratos FM, Rombouts K, Caplin M, Toumpanakis C, Thirlwell C, Mandair D. Neuroendocrine tumors and fibrosis: An unsolved mystery? Cancer. 2017;123:4770-90. doi:10.1002/CNCR.31079
14. Clement D, Ramage J, Srirajaskanthan R. Update on Pathophysiology, Treatment, and Complications of Carcinoid Syndrome. J Oncol. 2020;:8341426.doi:10.1155/2020/8341426
15. Cunningham JL, Janson ET, Agarwal S, Grimelius L, Stridsberg M. Tachykinins in endocrine tumors and the carcinoid syndrome. Eur J Endocrinol. 2008;159:275-82. doi:10.1530/EJE-08-0196
16. Hannah-Shmouni F, Stratakis CA, Koch CA. Flushing in (neuro) endocrinology. Rev Endocr Metab Disord. 2016;17:373-380. doi:10.1007/S11154-016-9394-8/FIGURES/2
17. Boutzios G, Kaltsas G. Clinical Syndromes Related to Gastrointestinal Neuroendocrine Neoplasms. Front Horm Res. 2015;44:40-57. doi:10.1159/000382053
18. Ikizoğlu G. Red face revisited: Flushing. Clin Dermatol. 2014;32:800-8. doi:10.1016/J.CLINDERMATOL.2014.02.019
19. Öberg K. 45 – Neuroendocrine Tumors and Related Disorders. 14th ed.

Amsterdam: Elsevier; 2020. doi:10.1016/B978-0-323-55596-8.00045-0
20. Ohe MR von der, Camilleri M, Kvols LK, Thomforde GM. Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. N Engl J Med. 1993;329:1073-8. doi:10.1056/NEJM199310073291503
21. Eads JR, Reidy-Lagunes D, Soares HP, Chan JA, Anthony LB, Halfdanarson TR, et al. Differential Diagnosis of Diarrhea in Patients With Neuroendocrine Tumors. Pancreas. 2020;49:1123-30. doi:10.1097/MPA.0000000000001658
22. Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J. Analysis of 150 Patients With Carcinoid Syndrome Seen in a Single Year at One Institution in the First Decade of the Twenty-First Century. Am J Cardiol. 2008;101:378-381. doi:10.1016/J.AMJCARD.2007.08.045
23. Zuetenhorst JM, Bonfrer JM, Korse CM, Bakker R, van Tinteren H, Taal BG. Carcinoid heart disease: The Role of Urinary 5-Hydroxyindoleacetic Acid Excretion and Plasma Levels of Atrial Natriuretic Peptide, Transforming Growth Factor-B and Fibroblast Growth Factor Johanna. Cancer. 2003;97:1609-1615. doi:10.1002/CNCR.11226
24. Bhattacharyya S, Toumpanakis C, Chilkunda D, Caplin ME, Davar J. Risk Factors for the Development and Progression of Carcinoid Heart Disease. Am J Cardiol. 2011;107:1221-6. doi:10.1016/J.AMJCARD.2010.12.025
25. Kaltsas G, Caplin M, Davies P, Ferone D, Garcia-Carbonero R, Grozinsky-Glasberg S, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors. Neuroendocrinology. 2017;105:245-54. doi:10.1159/000461583
26. Del Olmo-García MI, Muros MA, López-de-la-Torre M, Agudelo M, Bello P, Soriano JM, et al. Prevention and Management of Hormonal Crisis during Theragnosis with LU-DOTA-TATE in Neuroendocrine Tumors. A Systematic Review and Approach Proposal. J Clin Med. 2020;9:1-16. doi:10.3390/JCM9072203
27. Grozinsky-Glasberg S, Davar J, Hofland J, Dobson R, Prasad V, Pascher A, et al. European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome (CS) and Carcinoid Heart Disease (CHD). J Neuroendocrinol. 2022:e13146. doi:10.1111/JNE.13146
28. Corcuff JB, Chardon L, el Hajji Ridah I, Brossaud J. Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. Endocr Connect. 2017;6:R87-R98. doi:10.1530/EC-17-0071
29. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, et al. Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors: An Expert Statement. J Am Coll Cardiol. 2017;69(10):1288-1304. doi:10.1016/J.JACC.2016.12.030
30. Wedin M, Mehta S, Angerås-Kraftling J, Wallin G, Daskalakis K. The Role of Serum 5-HIAA as a Predictor of Progression and an Alternative to 24-h Urine 5-HIAA in Well-Differentiated Neuroendocrine Neoplasms. Biology. 2021;10:76. doi: 10.3390/biology10020076.
31. Becker A, Schalin-Jäntti C, Itkonen O. Comparison of Serum and Urinary 5-Hydroxyindoleacetic Acid as Biomarker for Neuroendocrine Neoplasms. J Endocr Soc. 2021;5:1-7. doi:10.1210/jendso/bvab106
32. Bober B, Saracyn M, Kołodziej M, Kowalski Ł, Deptuła-Krawczyk E, Kapusta W,~et al. Carcinoid Heart Disease: How to Diagnose and Treat in 2020? Clin Med Insights Cardiol. 2020;14. doi:10.1177/1179546820968101
33. Dimitriadis GK, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocrine-Related Cancer. 2016;23(9):R423-R436. doi:10.1530/ERC-16-0200
34. Bouma G, van Faassen M, Kats-Ugurlu G, de Vries EGE, Kema IP, Walenkamp AME. Niacin (Vitamin B3) Supplementation in Patients with Serotonin-Producing Neuroendocrine Tumor. Neuroendocrinology. 2016;103:489-94. doi:10.1159/000440621
35. Fiebrich HB, van den Berg G, Kema IP, Links TP, Kleibeuker JH, Van Beek AP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther. 2010;32:1398-404. doi:10.1111/J.1365-2036.2010.04479.X
36. Alonso-Gordoa T, Capdevila J, Grande E. GEP-NETs update: Biotherapy for neuroendocrine tumours. Eur J Endocrinol. 2015;172:R31-R46. doi:10.1530/EJE-14-0354
37. Kvols LK, Oberg KE, O'Dorisio TM, Mohideen P, de Herder WW, Arnold R, et al. Pasireotide (SOM230) shows efficacy and tolerability in the treatment of patients with advanced neuroendocrine tumors refractory or resistant to octreotide LAR: results from a phase II study. Endocr Relat Cancer. 2012;19:657-66. doi:10.1530/ERC-11-0367
38. Wolin EM, Jarzab B, Eriksson B, Walter T, Toumpanakis C, Morse MA, et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Devel Ther. 2015;9:5075-86. doi:10.2147/DDDT.S84177
39. Halperin DM, Huynh L, Beaumont JL, Cai B, Totev T, Bhak RH, et al. Impact of carcinoid syndrome symptoms and long-term use of somatostatin analogs on quality of life in patients with carcinoid syndrome A survey study. Medicine. 2018;97 :e13390.doi:10.1097/MD.0000000000013390
40. Blot K, Duchateau L, Lescrauwaet B, Liyanage N, Ray D, Mirakhur B, et al. A Patient-Reported Outcomes Analysis Of Lanreotide In The Treatment Of NETs Patients With Carcinoid Syndrome: Evidence From The ELECT Trial. Patient Relat Outcome Meas. 2019;10:335-43. doi:10.2147/PROM.S219982
41. Kulke MH, Hörsch D, Caplin ME, Anthony LB, Bergsland E, Öberg K, et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol. 2017;35:14-23. doi:10.1200/JCO.2016.69.2780
42. Cella D, Beaumont JL, Hudgens S, Marteau F, Feuilly M, Houchard A, et al. Relationship Between Symptoms and Health-related Quality-of-life Benefits in Patients With Carcinoid Syndrome: Post Hoc Analyses From TELESTAR. Clin Ther. 2018;40:2006-2020.e2. doi:10.1016/J.CLINTHERA.2018.10.008
43. Hörsch D, Anthony L, Gross DJ, Valle JW, Welin S, Benavent M, et al. Long-term treatment with telotristat ethyl in patients with carcinoid syndrome symptoms: results from the TELEPATH study. Neuroendocrinology. 2022;112:298. doi:10.1159/000516958
44. Saavedra C, Barriuso J, McNamara MG, Valle JW, Lamarca A. Spotlight on telotristat ethyl for the treatment of carcinoid syndrome diarrhea: patient selection and reported outcomes. Cancer Manag Res. 2019;11:7537-56. doi:10.2147/CMAR.S181439
45. Hofland LJ, de Herder WW, Waaijers M, Zuijderwijk J, Uitterlinden P, van Koetsveld PM, et al. Interferon-alpha-2a is a potent inhibitor of hormone secretion by cultured human pituitary adenomas. J Clin Endocrinol Metab. 1999;84:3336-43. doi:10.1210/JCEM.84.9.6005
46. Oleinikov K, Korach A, Planer D, Gilon D, Grozinsky-Glasberg S. Update in carcinoid heart disease - the heart of the matter. Rev Endocr Metab Disord. 2021;22:553-61. doi:10.1007/s11154-020-09624-y/Published
47. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with 177 Lu-Dotatate in the Phase III NETTER-1 Trial. J Clin Oncol. 2018;36:2578-84. doi:10.1200/JCO.2018.78.5865
48. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017;376:125-35. doi:10.1056/NEJMOA1607427
49. Cives M, Strosberg J. Radionuclide therapy for neuroendocrine tumors. Curr Oncol Rep. 2017;19:9. doi:10.1007/S11912-017-0567-8
50. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A, et al. 177Lu-Dotatate plus long-acting octreotide versus high dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22:1752-63. doi:10.1016/S1470-2045(21)00572-6
51. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968-77. doi:10.1016/S0140-6736(15)00817-X
52. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378:2005-12. doi:10.1016/S0140-6736(11)61742-X
53. Jin C, Nair A, Balasingam S, Majid M, Al Chalaby S, Takahashi N, et al. Carcinoid Heart Disease: Pathophysiology, Pathology, Clinical Manifestations, and Management. Cardiology. 2021;146:65-73. doi:10.1159/000507847
54. Davis LM, Nicou N, Martin W, Corcoran B, Mulholland N, Srirajaskanthan R, et al. Timing of peptide receptor radiotargeted therapy in relation to cardiac valve surgery for carcinoid heart disease in patients with neuroendocrine metastases and cardiac syndrome. A single-centre study from a centre of excellence. Nucl Med Commun. 2020;41:575-81. doi:10.1097/MNM.0000000000001200
55. Hicks RJ, Kwekkeboom DJ, Krenning E, Komminoth P, Kos-Kudła B, de Herder WWet al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Peptide Receptor Radionuclide Therapy with Radiolabelled Somatostatin Analogues. Neuroendocrinology. 2017;105:295-309. doi:10.1159/000475526

56. Bernheim AM, Connolly HM, Rubin J, Møller JE, Scott CG, Nagorney DM, et al. Role of Hepatic Resection for Patients With Carcinoid Heart Disease. Mayo Clin Proc. 2008;83:143-50. doi:10.4065/83.2.143
57. Bernheim AM, Connolly HM, Hobday TJ, Abel MD, Pellikka PA. Carcinoid Heart Disease. Progr Cardiovasc Dis. 2007;49:439-51. doi:10.1016/J.PCAD.2006.12.002
58. Askew JW, Connolly HM. Carcinoid valve disease. Curr Treat Options Cardiovasc Med. 2013;15:544-55. doi:10.1007/S11936-013-0265-2/FIGURES/1
59. Bonou M, Kapelios CJ, Kaltsas G, Perreas K, Toutouzas K, Barbetseas J. Cardiac surgery for carcinoid heart disease: a weapon not to be misused. Cardiology. 2017;136:243-51. doi:10.1159/000450938
60. Hart EA, Meijs TA, Meijer RCA, Dreijerink KM, Tesselaar ME, de Groot CA, et al. Carcinoid heart disease: a guide for screening and timing of surgical intervention. Neth Heart J. 2017;25:471-8. doi:10.1007/S12471-017-1011-2

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Artigo Revisão

Défice da Hormona do Crescimento no Adulto: Indicações e Posologia

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INFORMAÇÃO SOBRE O ARTIGO

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R E S U M O

A deficiência da hormona do crescimento pode desenvolver-se durante a infância ou a idade adulta, resultante de uma variedade de causas. Na infância tipicamente resulta num crescimento anormalmente lento e baixa estatura. Por sua vez, na idade adulta é caracterizada por alterações do metabolismo, da composição corporal, da função física e psicossocial, diminuição da qualidade de vida e um aumento da morbilidade e mortalidade cardiovascular. O tratamento com a reposição da hormona do crescimento melhora a maioria destas alterações. Em Portugal, os doentes adultos elegíveis para tratamento abrangem aqueles com uma deficiência isolada em somatropina com início na idade pediátrica e adultos com deficiência grave de somatropina no contexto de uma insuficiência hipofisária múltipla. O tratamento é fornecido gratuitamente pelo Sistema Nacional de Saúde. A aprovação para a prescrição hospitalar passa obrigatoriamente pelo parecer da Comissão Nacional para a Normalização da Hormona do Crescimento. Os riscos e benefícios da terapêutica devem ser sempre discutidos com cada doente.

Keywords:
Growth Disorders/drug therapy;
Human Growth Hormone/administration & dosage;
Human Growth Hormone/deficiency.

Growth Hormone Deficiency in Adults: Indications and Dosage

A B S T R A C T

Growth hormone deficiency can develop during childhood or adulthood, resulting from a variety of causes. In childhood it typically results in abnormally slow growth and short stature. In turn, in adulthood it is characterized by changes in metabolism, body composition, physical and psychosocial function, decreased quality of life and an increase in cardiovascular morbidity and mortality. Treatment with growth hormone replacement improves most of these changes. In Portugal, adult patients eligible for treatment include those with an isolated somatropin deficiency with pediatric onset and adults with severe somatropin deficiency in the context of multiple pituitary insufficiency. Treatment is provided free of charge by the National Health System. Approval for hospital prescriptions must be submitted by the National Commission for the Normalization of Growth Hormone. The risks and benefits of therapy should always be discussed with each patient.

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Introdução

Até 1985, a hormona do crescimento (HC) era escassa e somente usada para o tratamento de crianças com problemas de crescimento, sendo suspensa quando se atingia a estatura alvo pretendida.[1] Nos adultos, a reposição da HC permaneceu um tema alvo de controvérsia durante vários anos. O elevado custo da terapia, a disponibilidade reduzida, a dificuldade na realização de testes de estimulação e as preocupações inerentes a possíveis efeitos adversos a longo prazo foram alguns dos obstáculos que limitaram o seu uso.[2] Contudo, a evidência acumulada de benefícios na reversão de várias alterações metabólicas, fez com que se pensasse na sua reposição em determinados contextos.[2] Atualmente, o défice da HC no adulto é uma entidade clínica bem reconhecida com consequências adversas à saúde, que inclui alterações do metabolismo, da composição corporal, da função psicossocial e um aumento da morbilidade e mortalidade cardiovascular.[2-6] Em Portugal, desde 2017, a HC pode ser fornecida gratuitamente a adultos com défice da HC isolado de início na idade pediátrica e em indivíduos com défice da HC, no contexto de uma insuficiência adenohipofisária múltipla, após o parecer favorável da Comissão Nacional para a Normalização da Hormona do Crescimento (CNNHC).[7] Esta comissão foi criada em 1992 e compete-lhe a definição e a individualização das condições de administração da HC.[8]

Síntese da HC

A HC ou somatrofina é uma proteína com 191 aminoácidos, produzida pelas células somatotróficas na adeno-hipófise, sob influência de estímulos com origem no hipotálamo, no intestino, no fígado e nas gónadas.[9-12] A secreção da HC é caracterizada por pulsos episódicos ao longo do dia, intercalados com uma secreção basal mínima.[6,13] O principal pulso ocorre à noite, durante o sono profundo.[6,10] A nível do hipotálamo, são dois os peptídeos principais que a regulam: a hormona hipotalâmica estimuladora da HC (GHRH) ou somatorrelina e a hormona inibidora da libertação da HC ou somatostatina.[9,12] A síntese destas hormonas é influenciada por diversos neurotransmissores, tais como a serotonina, a dopamina, a acetilcolina e a noradrenalina e por hormonas periféricas, como a insulina e os glicocorticóides.[11,12] A grelina, oriunda do trato gastrointestinal e do núcleo ventromedial e arqueado do hipotálamo, vai atuar a nível do seu recetor hipotalâmico e em sinergismo com a GHRH, induzir a secreção da HC.[6,12,13] A maioria da HC circula ligada a proteínas de transporte específicas e apenas 20% circula na forma monomérica.[12] Os efeitos da HC podem resultar de uma ação direta, desencadeada pela sua ligação ao respectivo receptor na membrana plasmática ou serem mediados indirectamente pelo IGF-1.[11,12,14,15] Tanto o IGF-1 como a HC, exercem um mecanismo de *feedback* negativo a nível do hipotálamo, regulando a sua síntese. Outros fatores como a idade, o sexo, a puberdade, a alimentação, a atividade física, o estado nutricional e o índice de massa corporal também influenciam a sua secreção.[9-12] As mulheres apresentam níveis superiores de HC comparativamente a indivíduos do sexo masculino da mesma idade e estes são ainda afetados pela fase do ciclo menstrual, sendo mais elevados na fase lútea.[11,16] As concentrações da HC são mais elevadas no período neonatal imediato, diminuem ao longo da infância e aumentam novamente na puberdade, em consequência do aumento da amplitude dos pulsos. Posteriormente, há um decréscimo ao longo do processo de envelhecimento.[12,14]

Ação da HC

Os efeitos da HC são mediados essencialmente pelo IGF-1, produzido a nível hepático e que atua nos tecidos periféricos como cartilagem, músculo e osso, promovendo o crescimento linear (ação anabólica) (Tabela 1).[13] Os efeitos metabólicos ocorrem sobretudo pela ação direta da HC sobre o metabolismo dos hidratos de carbono, dos lípidos e das proteínas.[9,10,11,13,15]

Descoberta da HC

O estudo da hipófise iniciou-se pela curiosidade inerente à descrição de pessoas com gigantismo e características acromegálicas. Em 1912, Harvey Cushing concebe a existência da HC, descrevendo-a pela primeira vez no livro da sua autoria "A glândula hipofisária" e promovendo a partir daí, mais investigação nesta área.[6] A primeira metade do século XX é pautada por observações clínicas e estudos anatómicos e bioquímicos que permitiram formar a base para o entendimento da estrutura da HC e o conhecimento dos seus efeitos metabólicos.[17] Em 1922 é descrita por Evans e Long, o papel da glândula pituitária no crescimento, após observação de um crescimento excessivo em ratinhos, aos quais foi fornecido extracto de HC de origem bovina.[19] Este período, foi

Tabela 1. Efeitos fisiológicos da HC e do IGF-1.

	Ação da HC	**Ação do IGF-1**
Composição corporal	Diminuição da massa gorda, aumento da massa magra	Evidência conflituante- pode ter efeitos similares à HC
Desempenho físico	Aumento da massa e força muscular, aumento do VO2 máximo e da frequência cardíaca máxima	Aumento do VO2 máximo,
Efeito anabólico nos músculos respiratórios	Aumento da massa ventricular esquerda com aumento correspondente no débito cardíaco	Regulação dos tónus vascular. Níveis correlacionam-se com hemoglobina, potenciando a entrega de oxigénio
Alterações cardiovasculares	Aumento da massa ventricular esquerda com aumento correspondente no débito cardíaco	Regulação dos tónus vascular. Níveis correlacionam-se com hemoglobina, potenciando a entrega de oxigénio
Metabolismo da glicose	Induz insulinorresistência, reduz a captação periférica da glucose	Aumenta a sensibilidade à insulina a nível muscular e do tecido adiposo
Gordura	Lipólise com o aumento de ácidos gordos livres e glicerol	----
Proteínas	Aumenta síntese proteica	Aumenta síntese proteica
Osso	Aumento do crescimento longitudinal do osso, aumento da densidade mineral óssea	Aumento do crescimento longitudinal do osso

HC: hormona do crescimento; IGF-1: fator de crescimento tipo insulina I; VO2: volume de oxigénio máximo.

dedicado à purificação de preparações da HC de diferentes espécies e à sua testagem em animais e humanos. Em 1932, Engelbach inicia a reposição com HC de origem animal em crianças, contudo sem sucesso, dada a especificidade da HC humana, que apenas foi reconhecida anos mais tarde, em 1956, por Ernest Knobil. Nesse ano, a HC humana é isolada no laboratório pela primeira vez por Li e Papkoff na Califórnia e por Raben em Massachussetts.[17] O período seguinte (1958-1985), durante o qual a HC humana derivada da hipófise foi usada, gerou um conhecimento mais aprofundado sobre o seu papel fisiológico e permitiu o seu uso em crianças.[6,17] Contudo, dada a sua disponibilidade reduzida, o seu uso era limitado e as crianças não podiam ser tratadas continuamente, definindo-se um limite de altura de 152 cm.[17,18] Em 1961, é fundada nos Estados Unidos da América, a Agência Nacional da Hipófise, uma organização responsável por colectar as glândulas pituitárias a partir de cadáveres e pela sua distribuição, combatendo assim o mercado negro que havia surgido. Outros países seguiram este exemplo.[18] Entre 1963 e 1985, 27 000 crianças foram tratadas a nível mundial com HC humana, com excelentes resultados. Porém em 1985, a Food and Drug Administration (FDA) foi notificada de quatro casos de jovens adultos com doença de Creuzfeldt Jacob, receptores de HC de origem humana na década de 1960.[17] A conexão com a toma da HC na infância foi reconhecida e a sua distribuição suspensa.[17] A era seguinte caracterizou-se pela identificação da estrutura bioquímica da HC e pelo surgimento da tecnologia recombinante que permitiu a simplificação da sua produção, a distribuição em larga escala e eliminou os riscos inerentes ao uso de derivados da hipófise humana.[6,20] É também reconhecido o benefício da HC recombinante em distúrbios que não o défice da HC. O tratamento com HC para adultos foi aprovado pela FDA em 1996.[6,17] Em Portugal em 2010, foi aprovada a indicação para adultos com défice da HC diagnosticada na infância e em 2017, foi revisto o seu uso na população adulta.

Manifestações clínicas

As manifestações clínicas do défice da HC são variáveis e dependem de vários fatores: a idade de início, a intensidade do défice hormonal, o tempo decorrido desde o início da patologia, a etiologia e a concomitância com outros défices hormonais.

No período neonatal o sintoma mais frequente é a hipoglicemia, que pode associar-se a convulsões. O recém-nascido pode apresentar-se hipotérmico, com hiperbilirrubinemia conjugada e prolongada e os meninos podem apresentar um micropénis.[21]

Na criança e adolescente pode manifestar-se por diminuição na velocidade de crescimento, baixa estatura, implantação anómala dos dentes e adiposidade troncular.[13,14]

No adulto caracteriza-se por sintomas e sinais inespecíficos: astenia, depressão, labilidade emocional, redução da massa magra, da força muscular, aumento da massa gorda, osteoporose, esteatose hepática, aumento do colesterol total, das lipoproteínas de baixa densidade (LDL) e diminuição moderada das lipoproteínas de alta densidade (HDL) (Tabela 2).[3,19,22] A maior morbimortalidade cardiovascular relaciona-se, pelo menos em parte, à alta prevalência da síndrome metabólica.[13] As alterações do metabolismo dos hidratos de carbono são mais comuns em indivíduos obesos e verificam-se nos indivíduos com índice de massa corporal (IMC) normal de forma proporcional à adiposidade central. O excesso de massa gorda parece ser a principal causa destas disfunções.[22] Apesar da heterogeneidade nos estudos, as alterações ósseas incluem modificações na remodelação óssea e diminuição da densidade mineral com aumento do risco de osteoporose e fratura.[22,23] Os doentes auto-percepcionam terem menos saúde e menos energia do que os indivíduos saudáveis da mesma idade e aqueles com início na infância e persistência na idade adulta têm manifestações clínicas geralmente mais acentuadas.[24,25]

Etiologia

O défice da HC no adulto é frequentemente associado a lesões ocupantes de espaço na região hipotálamo-hipofisária e/ou relaciona-se com o tratamento desses tumores, na sequência de cirurgia ou radioterapia.[2,4,10,26] Outras causas encontram-se descritas na Tabela 3. A secreção da HC é tipicamente a primeira a ser afetada na maioria dos casos de hipopituitarismo.[26,27] Quando a deficiência ocorre na infância devido a uma causa orgânica, esta quase sempre persiste no adulto.[28] Em contraste, a deficiência idiopática raramente persiste, não estando claro se o diagnóstico foi erróneo ou se tratou de uma forma parcial ou transitória de défice da HC.[28,29] Podemos assim estabelecer três grupos de indivíduos adultos: aqueles com diagnóstico prévio de défice da HC de início na infância, défice da HC adquirido e secundário a lesões estruturais ou trauma e aqueles com défice idiopático.

Diagnóstico

Dada a inespecificade da sintomatologia no adulto, o diagnóstico pode ser um desafio.[10] A decisão de testar para o défice da HC deve ser baseada num contexto clínico apropriado, com uma elevada probabilidade pré teste e quando existe intenção de tratamento.[2,16,30] O diagnóstico requer assim a integração da história clínica e de parâmetros laboratoriais e imagiológicos. O indivíduo deve ser questionado sobre o seu crescimento (observando-se se possível o boletim infantil de saúde) e sintomas sugestivos de outros défices hormonais.[31] Antecedentes de exposição a radiação craniana, défice da HC na infância, história de traumatismo craniano ou infeção do sistema nervoso central, consanguinidade e/ou um membro da família afetado devem também ser inquiridos. Características dismórficas, particularmente defeitos da linha média craniofacial, podem alertar para o atingimento da hipófise.[14,21] Mas o exame físico pode não revelar nenhum achado significativo.[16] A investigação laboratorial baseia-se na determinação do

Tabela 2. Manifestações clínicas da deficiência da HC.

Deficiência hormonal de HC	Sinais e sintomas
Período neonatal	Micropénis, hipoglicemia, hiperbilirrubinemia conjugada e prolongada
Crianças	Atraso na velocidade de crescimento, atraso na maturação óssea, baixa estatura, implantação anómala dos dentes, adiposidade abdominal, hipotrofia muscular.
Adultos	Fraqueza, depressão, osteoporose, labilidade emocional, redução na massa magra e na capacidade para o exercício, aumento da massa gorda (com distribuição predominantemente troncular), esteatose hepática, aumento do colesterol LDL e aumento do risco de doença cardiovascular

Adaptada de Vilar L. Endocrinologia Clínica. 7ª ed. São Paulo: Guanabara Koogan; 2020.[13]
HC: hormona do crescimento; LDL: lipoproteínas de baixa densidade.

Tabela 3. Causas de deficiência da HC.

Congénita
• Defeitos dos fatores de transcrição (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2), mutações nos genes da HC, do recetor do GHRH • Mutações no receptor da HC - Síndrome de Laron (Nanismo por insensibilidade à hormona do crescimento) • Defeitos estruturais: agenesia do corpo caloso, displasia septo-óptica, hidrocefalia, quisto aracnóide, Síndrome da sela turca vazia
Adquirida
• Tumores da região hipotálamo-hipófise - adenoma hipofisário - craniofaringeoma - quisto da bolsa de Rathke - glioma/astrocitoma - germinoma - cordoma - meningioma - metástase • Doenças infiltrativas/granulomatosas (sarcoidose, tuberculose, hemocromatose, histiocitose de células de Langerhans) • Doenças inflamatórias (hipofisite) • Induzida por fármacos (inibidores do checkpoint imunitário, interferon-α, quimioterápicos) • TCE • Hemorragia subaracnoideia • Acidente vascular cerebral • Infeções do sistema nervoso central (meningite, encefalite) • Síndrome de Sheehan • Pós-cirurgia da região hipotálamo-hipófise • Pós-radioterapia • Apoplexia hipofisária • Idiopática

Adaptada de Yuen KC, *et al*. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult Care. Endocr Pract. 2019;25:1191-232.2
HC: hormona do crescimento; GHRH: hormona hipotalâmica estimuladora da secreção da hormona do crescimento; TCE: traumatismo crânio-encefálico.

IGF-1 e nos testes de estimulação da HC.[13,19] Os níveis basais de HC são pouco úteis, dada a sua secreção pulsátil e semivida curta.[9,32] Por sua vez, o IGF-1 varia relativamente pouco ao longo do dia e a interpretação do seu nível deve ser adaptada ao género e à idade.[2,8] A presença de um IGF-1 baixo aumenta a probabilidade de défice da HC, mas não confirma o diagnóstico, uma vez que pode ser encontrado perante outras condições (desnutrição, doença hepática, hipotiroidismo, doença sistémica ou diabetes *mellitus* (DM) mal controlada).[4,10,11,13] O IGF-1 tem também um baixo valor diagnóstico particularmente em adultos acima de 40 anos, dada a sobreposição dos níveis entre indivíduos saudáveis e com défice da HC.[2,14,22] Por outro lado, em até 30% dos casos de défice da HC, o IGF-1 pode ser normal.[4,13,32] Mas se a suspeita clínica permanecer alta, os testes diagnósticos devem ser realizados. Perante um indivíduo bem nutrido e sem doença hepática, um IGF-1 baixo (< –2 desvio padrão) e pelo menos três deficiências hormonais pituitárias (não incluindo a HC), existe uma forte evidência de défice da HC. Neste contexto, alguns autores, consideram a realização de testes de estimulação opcionais, enquanto outros defendem a realização de pelo menos um teste para confirmar o diagnóstico.[16] No caso de suspeita de défice isolado da HC ou hipopituitarismo parcial (uma suspeita de défice da HC mais um défice hormonal hipofisário adicional), os doentes devem ser submetidos a dois testes provocativos para estabelecer o diagnóstico, particularmente se o IGF-1 não for baixo.[16,50] Estas provas devem ser efetuadas numa unidade de Endocrinologia com experiência na sua realização.[4,10] Para indivíduos com diagnóstico de défice da HC "de novo", o passo seguinte consiste na realização de uma RM da hipófise.[29] A investigação genética não é realizada por rotina, à excepção de um quadro clínico característico: uma falha no crescimento precoce, história familiar positiva, altura mais do que 3 desvio padrão abaixo da média, valores de resposta aos testes de estimulação da HC e níveis de IGF-1 muito baixos.[14]

Testes de estimulação

O diagnóstico do défice da HC exige a demonstração de um aumento subnormal do pico sérico da HC em resposta a um ou mais testes de estimulação. Atualmente, são vários os testes disponíveis, enfatizando a complexidade envolvida na realização de um diagnóstico preciso.[16] Nenhum deles é ideal e a escolha deve ter em consideração características individuais e a sua validade.[10,16,33] O teste de tolerância à insulina (TTI) é considerado o teste de eleição pelas principais directrizes internacionais.[10,16] Caso contra-indicação, o teste com glucagon pode ser utilizado como alternativa.[16,32] O teste combinado de GHRH e arginina, foi no passado também realizado, contudo a descontinuação da produção do análogo GHRH em 2008, levou à sua suspensão.[30] O teste de clonidina não é útil nos adultos, dado ser um secretagogo fraco.[16] Os testes de estimulação apresentam várias ressalvas: a variabilidade inter-individual, os diferentes pontos de corte da HC dependendo do teste usado, a relativa falta de dados normativos validados com base na idade, no sexo, no IMC, na homeostase da glicose e para as diversas etiologias do défice da HC.[2,29] Falsos positivos podem ser observados em indivíduos obesos e idosos.[10] Com a idade, há um declínio na produção da HC. No caso da obesidade, esta corresponde a um estado de défice da HC funcional, caracterizando-se por uma diminuição da secreção espontânea e estimulada da HC, pelo que devem ser considerados pontos de corte específicos de acordo com o IMC. A patogénese da redução da secreção da HC na obesidade é desconhecida.[16] Os níveis de IGF-1 não são afetados, e acredita-se que essa discordância entre HC e IGF-1 seja o resultado do aumento da sensibilidade hepática à HC. Os testes de estimulação devem ser assim evitados em indivíduos obesos com baixa probabilidade pré-teste. A questão sobre qual o teste de estimulação que deve ser usado num indivíduo obeso não pode ser respondida de forma geral. O Endocrinologista deve ter em consideração as ressalvas de cada teste e interpretar os resultados, contextualizando com outros parâmetros, nomeadamente com os valores IGF-1 ou a presença ou ausência de outras deficiências hormonais pituitárias. Caso deficiência de uma ou mais hormonas hipofisárias, é necessário a sua reposição antes da realização de qualquer teste.[16] Foi também descrita uma variabilidade significativa entre os doseamentos da HC obtidos com diferentes imunoensaios.[16,34] A HC circulante está presente em várias isoformas, incluindo a variante mais comum de 22 kDa e outras moléculas menores, como a variante de 20 kDa.[33] Um método analítico específico para a deteção da isoforma de 22 kDa é recomendado, mas muitos ensaios ainda contêm anticorpos que detectam outras formas circulantes.[16] Outras moléculas semelhantes, como a HC placentária e a prolactina podem reagir cruzadamente e afetar o doseamento da HC. Neste sentido, todos os métodos analíticos devem especificar a validação do seu ensaio, incluindo a especificação das isoformas detectadas, as especificidades dos anticorpos utilizados e a presença ou ausência de interferência proteica.[16,33]

Teste de tolerância à insulina

A fundamentação deste teste reside no facto da insulina, ao provocar hipoglicemia, desencadeia por estimulação α-adrenérgica, a secreção de GHRH e HC, ACTH e cortisol. O procedimento exige jejum de pelo menos 8 horas e consiste na administração endovenosa de insulina regular: indivíduos saudáveis: 0,10 U/kg; estados de insulinorresistência, como na obesidade: 0,2 U/kg. Deve efetuar-se colheita de sangue aos 0, 30, 60, 90 e 120 minutos e avaliar a glicemia capilar, HC e cortisol séricos em todos os tempos.

Interpretação:

- Estímulo válido de secreção HC: glicemia <40 mg/dL.
- Défice de HC nos adultos: pico de resposta [HC] ≤5 µg/L.[2,10]
- Défice da HC grave: [HC] ≤3 µg/L

Limitações: Perante uma DM descompensada, a prova não é interpretável. Pode ocorrer hipoglicemia tardia.[10,30] Dada a hipoglicemia e o risco de convulsão, há necessidade de supervisão médica.[16] Está contra-indicada se antecedentes de convulsão/epilepsia, patologia cardíaca isquémica ou cerebrovascular, gravidez e nos idosos.[16] Na maioria dos estudos realizados com o TTI, nunca foi proposto um ponto de corte da HC relacionado com o IMC.[35] Nalguns estudos, foi demonstrado que um *cut off* de 3 µg/L permite a distinção entre indivíduos saudáveis e com défice da HC, mesmo perante condições que resultem numa redução da sua secreção, como a idade e a obesidade.[16] Em 2020, o Departamento de Endocrinologia, Diabetes e Metabolismo de Turin publicou um estudo com doentes com antecedentes de doença hipotálamo-hipofisária em que definiu o ponto de corte da HC no TTI de acordo com o IMC: 3,5 µg/L em indivíduos com IMC < 25 kg/m² (sensibilidade 82,1%, especificidade 85,7%), 1,3 µg/L em indivíduos com excesso de peso (sensibilidade 74,1%, especificidade 85,7%) e 2,2 µg/L em indivíduos obesos (sensibilidade 90,0%, especificidade 50,0%).[35] Os autores ressalvam contudo que o ponto de corte identificado em indivíduos com excesso de peso e obesos é caracterizado por uma acuidade diagnóstica muito reduzida, pelo que consideram que o TTI pode não representar a ferramenta diagnóstica de primeira escolha nestes indivíduos.[35] Mais estudos são necessários nesta área.

Teste de estimulação com glucagon

O mecanismo pelo qual o glucagon estimula a secreção de HC é mal compreendido.[34] O procedimento deve ser realizado em jejum de pelo menos 8 horas e consiste em colher sangue aos 0 minutos, seguida da administração intramuscular de 1-1,5 mg de glucagon (≤90 kg: 1 mg; >90 kg: 1,5 mg). De seguida, devem ser efetuadas colheitas aos 30, 60, 90, 120, 150, 180, 210 e 240 minutos e avaliação da glicemia capilar, cortisol e HC séricos em todos os tempos.[34]

Considera-se défice de HC nos adultos[2]:

- [HC] <3 µg/L
  1. IMC <25 kg/m²;
  2. 25 kg/m²≤ IMC ≤30 kg/m² se elevada suspeita clínica.
- [HC] <1 µg/L
  1. 25 kg/m²≤ IMC ≤30 kg/m² se baixa suspeita clínica;
  2. IMC >30 kg/m².

Este teste tem uma sensibilidade e especificidade de 100% em indivíduos normo- ponderais, é mais seguro nos idosos e tem uma menor variabilidade com o género e o ciclo menstrual.30 Limitações: Necessidade de múltiplas colheitas. Pode desencadear cefaleias, diaforese, cólicas abdominais, náuseas, vómitos,10,16 hipotensão grave, hipoglicemia e convulsões.[30] A resposta da HC ao glucagon pode ser mais atenuada pela idade e pela obesidade em comparação com o TTI.[16] Em pacientes com intolerância à glicose, a precisão diagnóstica deste teste permanece incerta.[2] A hiperglicemia foi associada com uma menor resposta de pico da HC, mas mais estudos prospectivos são necessários.[34]

Teste de estimulação com macimorelina

A macimorelina é um agonista sintético do receptor da grelina, capaz de estimular a secreção da HC.[10,32,36] Está disponível na forma de grânulos que são dissolvidos em água e tomados por via oral. A dose recomendada é de 0,5 mg/kg. De seguida, são recolhidas quatro amostras de sangue aos 30, 45, 60 e 90 minutos.10,33 Um aumento subnormal na concentração sérica da HC (<2,8 µg/L) confirma o défice da HC.[33] Este parece ser um teste promissor e atraente pela simplicidade na sua realização, alta reprodutibilidade, segurança e melhor tolerabilidade.[33,36,37] Limitações: Os efeitos secundários incluem um sabor amargo/metálico, cefaleias, náuseas, tonturas e diarreia.[33] Deve evitar-se o uso concomitante com indutores do CYP3A4 e fármacos que prolonguem o intervalo QT.[10,33] Mais estudos com idosos, obesos, DM e doenças renais ou hepáticas, são necessários para determinar a sua sensibilidade e especificidade nestas populações.[34,37] Uma saqueta de macimorelina de 60 mg custa aproximadamente 4150 euros.[13,33] Ainda não se encontra disponível em Portugal.

Quem deve ser avaliado

Segundo as recomendações do Consenso para o Diagnóstico e Tratamento com Défice da HC no Adulto de 2007, os indivíduos que devem ser testados incluem aqueles com evidência de doença hipotálamo-hipofisária e nos quais há intenção de tratar[4,10]:

1. Indivíduos com sinais e sintomas de doença hipotálamo-hipofisária
2. Indivíduos que realizaram radioterapia craniana ou cirurgia envolvendo a região hipotálamo-hipofisária
3. Indivíduos com TCE ou hemorragia sub-aracnóide
4. Indivíduos com antecedentes de défice da HC na infância, na fase de transição para a idade adulta

A directriz da Endocrine Society de 2011 para a avaliação e tratamento do défice da HC no adulto recomenda que indivíduos com défice da HC prévio na infância sejam submetidos a uma reavaliação do eixo somatotrófico na fase de transição, após suspensão da terapêutica pelo menos um mês. Perante a combinação de uma doença hipofisária ou hipotalâmica ou com uma causa genética conhecida, múltiplas (≥3) deficiências hormonais hipofisárias e uma concentração subnormal do IGF-1 (< -2 Z *score* do desvio padrão), pode estabelecer-se o diagnóstico de défice da HC, sem necessidade de realizar os testes adicionais.[5,9,19,29,38] Caso etiologia idiopática, são recomendados dois testes para corroborar o diagnóstico.[10] A maioria das crianças quando retestadas têm uma função somatotrófica normal, sem a necessidade de manter a reposição.[16] Para indicações pediátricas não- défice da HC, incluindo a deficiência do gene *SHOX*, tamanho pequeno para idade gestacional em pacientes que não alcançam os percentis normais de crescimento, insuficiência renal crónica, síndrome de Turner ou Noonan e baixa estatura idiopática, a HC é geralmente interrompida quando o crescimento linear é atingido, com excepção do síndrome de Pradder Willi (SPW), que pode apresentar um défice de HC. No caso do SPW, os adolescentes que param o tratamento pioram ao longo do tempo relativamente aos parâmetros de composição corporal. Assim, se com o tratamento com somatrofina se notarem melhorias, ou pelo menos estabilização, o tratamento é mantido na idade adulta para regular a composição corporal.[39,40]

Indicações e contra-indicações para o uso da HC

Segundo as indicações da CNNHC de 2020, a HC pode ser fornecida a doentes com défice da HC grave e com repercussão na qualidade de vida (QV).[41]

Com base na evidência disponível, a definição de deficiência grave deve ser estabelecida de acordo com os seguintes pressupostos:

1. Na presença de lesões estruturais irreversíveis hipotálamo-hipofisárias acompanhadas de hipopituitarismo, com pelo menos 3 défices estabelecidos das hormonas segregadas na hipófise (da HC e outras duas hormonas) e níveis de IGF-1 inferiores aos valores de referência para a idade e género (< -2DP).
2. Perante um quadro clínico compatível com défice da HC na sequência de traumatismo crânio-encefálico ou hemorragia sub-aracnoideia.
3. Existência de défice da HC diagnosticado na infância e persistente na idade adulta.

A terapêutica está contraindicada se doença maligna ativa, retinopatia diabética proliferativa ou não proliferativa, hipertensão intracraniana benigna, DM mal controlada, obesidade grau 3, apneia do sono não tratada, psicose ativa, insuficiência hepática ou renal, gravidez e nos idosos (estas duas últimas não são consensuais na literatura).[4,13,41]

Benefícios e riscos

Em vários estudos, a reposição da HC demonstrou efeitos benéficos a nível da composição corporal, da QV, da capacidade de exercício, na integridade esquelética e na melhoria dos biomarcadores cardiovasculares.[2,4,5,38] Polimorfismos a nível do recetor da HC podem influenciar a resposta individual ao tratamento.[37] O seu uso é considerado seguro.[2,4] Dado o risco da HC induzir insulinorresistência, em doentes diabéticos pode ser necessário proceder ao ajuste da terapêutica hipoglicemiante.[38] A decisão de iniciar/manter a terapêutica deve ser partilhada com o doente, equacionando sempre os benefícios e riscos (Tabela 4).[38] Em países como a Alemanha, Brasil, Dinamarca e Holanda, a melhoria da QV foi quantificada atráves da aplicação de um questionário – "Avaliação da QV no défice da HC do Adulto" (QOL-AGHDA).[42-44] Em Portugal, não existe nenhum questionário validado na língua portuguesa para avaliar a QV nestes pacientes. A adição destes questionários seria uma mais-valia na prática clínica.

Formulações da HC

Em Portugal, são comercializadas soluções injetáveis de HC de administração diária (Tabela 5), não havendo diferenças entre si. A toma deve ser à noite, de forma a simular a maior secreção fisiológica da HC.[4] Os custos podem alcançar os 6800 a 9 104 euros/ano para um doente com uma dose média de 0,5 mg/dia.[2,46] Apesar da elevada quantia, um estudo realizado na Suécia em 2013 relata que esta é uma terapia economicamente rentável, quando se considera a morbilidade e a mortalidade associadas ao défice da HC.[47] O facto da injeção ser diária pode tornar-se inconveniente a longo prazo.[37,45] Nos últimos anos, alguns laboratórios têm-se dedicado à síntese de formulações da HC de longa duração que vão permitir reduzir a frequência da toma para semanal, quinzenal ou mensal e desta forma, melhorar a adesão terapêutica.[45-49]

Dose e titulação

Segundo as indicações da CNNHC, a dose inicial de HC deve ser:

a) > 60 anos: 0,1- 0,2 mg/dia;
b) 30-60 anos: 0,2- 0,3 mg/dia;
c) < 30 anos: 0,4- 0,5 mg/dia;
d) Em doentes com DM ou anomalia da glicemia em jejum, iniciar com 0,1-0,2 mg/dia.

A dose é titulada gradualmente, a cada 4-6 semanas, até à normalização de IGF-1 sérico para a idade e sexo e posteriormente a avaliação é semestral.[20,38] Alguns estudos indicam que este deve ser mantido entre o valor médio e o limite superior da normalidade.[4,5] Em média, indivíduos do sexo masculino necessitam de 0,43 mg/dia e do sexo feminino de 0,53 mg/dia.[13] A dose de

Tabela 4. Benefícios e riscos associados à terapêutica com HC.

	Benefícios	Riscos
Composição corporal	Redução da massa gorda, aumento da massa magra, aumento da força muscular	Aumento do IMC, perímetro abdominal e aumento do índice cintura-anca
Metabolismo ósseo	Aumento da DMO	Efeito sobre incidência de fraturas não foi demonstrado
Qualidade de vida relacionada com a saúde	Melhor em questionários de qualidade de vida	Não há melhoria em todos os parâmetros relacionados com a qualidade de vida. Provável ausência de efeitos em doentes com qualidade de vida normal.
Marcadores de risco cardiovasculares	Aumento do colesterol HDL Redução do colesterol total e LDL Redução da pressão arterial diastólica Redução da PCR Redução da espessura da íntima-média carotídea	Redução da sensibilidade à insulina Aumento da glicemia e insulinemia Tendência a aumento da síndrome metabólica Aumento da lipoproteína (a)
Eventos cardiovasculares	Redução da incidência de enfartes agudos do miocárdio	Tendência a um aumento dos AVC
Neoplasias	Não aumenta a taxa de recidiva ou progressão dos tumores hipotálamo-hipofisários. Não aumenta o risco global de neoplasias.	Tendência a um aumento do risco de neoplasias em sobreviventes de cancro infantil tratados com HC na infância.
Mortalidade	Tendência a diminuição da mortalidade global e cardiovascular	Persistência de maior mortalidade em relação à população geral em alguns estudos

Adaptada de: Díez JJ, *et al*. Benefits and risks of growth hormone in adults with growth hormone deficiency. Med Clín. 2014; 21;143:354-9.3
HC: hormona do crescimento; DMO: densidade mineral óssea; PCR: proteína C reativa; IMC: índice de massa corporal; AVC: acidente vascular cerebral..

Tabela 5. Formulações disponíveis em Portugal.

	Titular	Dosagens disponíveis	Frequência da administração	Via de administração	Apresentação	Custos por caneta
Genotropin®	Laboratórios Pfizer, Lda.	5; 5,3; 12 mg/1 mL	Diária	Subcutânea	Caneta pré cheia; cartucho	130,08€
Norditropin Nordiflex ®	Novonorisk A/S	10; 15 mg/1,5 mL	Diária	Subcutânea	Caneta pré cheia	250,60€; 369,69€
Saizen® Saizen "Click Easy"®	Merck, S.A.	5,83; 8 mg/mL 8 mg/1,37 mL	Diária	Subcutânea; via intramuscular	Cartucho	138.71 €- 264.69 €
Humatrope®	Lilly-Portugal, Produtos Farmacêuticos, Lda.	12; 24 mg/3,15 mL 6 mg/3,17 mL	Diária	Subcutânea; via Intramuscular	Cartucho	369,69€
Omnitrope®	Sandoz GmbH	5; 10 mg/1,5 mL	Diária	Subcutânea	Caneta pré cheia	111,88€; 209,54€
Zomacton®	Ferring Portuguesa Lda	4 mg/3,5 mL	Diária	Subcutânea	Frasco	271,87 €
NutropinAq®	Ipsen TLD	10 mg/2 mL	Diária	Subcutânea	Cartucho	363,92€

manutenção raramente excede 1 mg/dia.[13] Não é recomendada a determinação da dose baseada no peso corporal, dada a variabilidade inter-individual na absorção, na sensibilidade à HC e na falta de evidências de que uma dose de reposição maior seja necessária em indivíduos com um maior IMC.[2,45] Os efeitos secundários do uso de HC recombinante incluem: edemas periféricos, cefaleias, artralgias, síndrome do túnel cárpico, mialgias e parestesias. São geralmente auto-limitados, dose dependentes e podem requerer redução da dose.[3,13] As mulheres devem preferir preparações transdérmicas ou transvaginais de estrogénio, pois a toma oral antagoniza os efeitos da HC, sendo necessário o uso de doses mais elevadas, o que aumenta o custo do tratamento.[13]

Monitorização

No caso de ajuste da dose da HC, a avaliação deve ser realizada não antes de 6 semanas após a alteração.[4] Deve também ser monitorizada a glicose em jejum, a hemoglobina glicada e o perfil lipídico periodicamente (a cada 6-12 meses) ou após alteração da dose.[5] As funções tiroideia e adrenal devem também ser vigiadas.[13,38] A HC causa redução da T4 livre, associada ou não à elevação dos níveis de T3. Assim, 36% a 47% dos pacientes previamente eutiroideus podem necessitar da reposição de levotiroxina após a introdução da HC.[13] No défice da HC observa-se um aumento da atividade da 11β-hidroxiesteroide desidrogenase tipo 1 (HSD11B1), enzima que converte a inativa cortisona em cortisol. Com a reposição da HC, cessa a hiperatividade da HSD11B1 e o hipocortisolismo pode tornar-se evidente.[13] A avaliação da composição corporal através de medidas antropométricas deve ser realizada pelo menos anualmente. A densitometria óssea deve ser realizada no início do estudo e a cada 2 anos.[4] Em doentes com história prévia de tumores da região hipotálamo-hipófise e com doença residual, a ressonância magnética (RM) deve ser realizada 6 meses após o início da terapêutica. Na ausência de tumor residual, a RM deve ser realizada 12 meses após.[5]

Conclusão

O diagnóstico de défice da HC na população adulta é um desafio. A decisão de testar deve ser baseada num contexto clínico apropriado, com uma elevada probabilidade pré teste e quando existe intenção de tratamento. O diagnóstico requer a integração da história clínica e de parâmetros laboratoriais e imagiológicos. Esta terapêutica está associada a um custo elevado para o sistema de saúde, devendo ser equacionados os benefícios e riscos para o indivíduo.

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References / Referências

1. Vageesh SA. History of growth hormone terapy. Indian J Endocrinol Metab. 2011; 15:162-5. doi: 10.4103/2230-8210.84852.
2. Yuen KC, Biller BM, Radovick S, Carmichael JD, Jasim S, Pantalone KM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult Care. Endocr Pract. 2019;25:1191-232. doi: 10.4158/GL-2019-0405.
3. Díez JJ, Cordido F. Benefits and risks of growth hormone in adults with growth hormone deficiency. Med Clín. 2014; 21;143:354-9. doi: 10.1016/j.medcli.2013.11.026.
4. Ho KK, 2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association

with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia, European Journal of Endocrinology. Eur J Endocrinol. 2007;157: 695-700. doi: 10.1530/EJE-07-0631.

5. Díez JJ, Sangiao-Alvarellos S, Cordido F. Treatment with Growth Hormone for Adults with Growth Hormone Deficiency Syndrome: Benefits and Risks. International Journal of Molecular Sciences. 2018;19(3):893. doi: 10.3390/ijms19030893.
6. Ranke MB, Wit JM. Growth hormone - past, present and future. Nat Rev Endocrinol. 2018;14:285-300. doi: 10.1038/nrendo.2018.22.
7. Dre.pt [homepage na Internet]. Portugal: Diário da República n.º 75/2019, Série I de 2019-04-16. Disponível em: https://data.dre.pt/eli/port/117/2019/04/16/p/dre/pt/html.
8. Dre.pt [homepage na Internet]. Portugal: Diário da República n.º n.º 32/2018, Série II de 2018-02-14. Disponível em: https://dre.tretas.org/dre/3244182/despacho-1569-2018-de-14-de-fevereiro.
9. Olarescu NC, Gunawardane K, Hansen TK, Møller N, Jørgensen JO. Normal Physiology of Growth Hormone in Adults. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al, editors. Endotext [Internet]. South Dartmouth: MDText.com, Inc.; 2000. [consultado 2021 Apr 22]. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK279056/.
10. Melmed S. Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. New Engl J Med. 2019; 380: 2551-62. doi: 10.1056/NEJMra1817346.
11. Cruzat VF, Júnior JD, Tirapegui J, Schneider CD. Hormônio do crescimento e exercício físico: considerações atuais. Rev Brasil Ciências Farmacêuticas. 2008;44:549-62. doi: 10.1590/S1516-93322008000400003.
12. Nicholls AR, Holt RI. Growth Hormone and Insulin-Like Growth Factor-1. Front Horm Res. 2016; 47:101-14. doi: 10.1159/000445173.
13. Vilar L. Endocrinologia Clínica. 7ª ed.São Paulo: Guanabara Koogan; 2020.
14. Jantarada CP. Deficiência da hormona de crescimento- Análise retrospetiva da casuística da Consulta de Endocrinologia Pediátrica do Centro Hospitalar do Porto. 2015 [consultado 2022 Abr 22]. Disponível em: https://repositorio-aberto.up.pt/bitstream/10216/81742/2/37487.pdf.
15. Bidlingmaier M, Strasburger CJ. Growth hormone. Handb Exp Pharmacol. 2010;195:187-200. doi: 10.1007/978-3-540-79088-4_8.
16. Glynn N, Agha A. Diagnosing growth hormone deficiency in adults. Int J Endocrinol. 2012; 2012:972617. doi:10.1155/2012/972617.
17. Ayyar VS. History of growth hormone therapy. Indian J Endocrinol Metab. 2011; 15 :162-5. DOI:10.4103/2230-8210.84852.
18. Cohen LE. Discovery of Growth Hormone and Synthesis of Recombinant Human Growth Hormone. In: Cohen LE, editor. Growth Hormone Deficiency: Physiology and Clinical Management. 1st ed. Zurich: Springer; 2016. p.1-4.
19. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Hassan MM, Salvatori R, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016; 101:3888–921. doi: 10.1210/jc.2016-2118.
20. Cai Y, Xu M, Yuan M, Liu Z, Yuan W. Developments in human growth hormone preparations: sustained-release, prolonged half-life, novel injection devices, and alternative delivery routes. Int J Nanomed. 2014; 9:3527-3538. doi: 10.2147/IJN.S63507.
21. Ogilvy-Stuart A. Growth Hormone Deficiency from Birth to 2 Years of Age: Diagnostic specifics of GHD during the early phase of life. Horm Res. 2003; 60: 2-9. doi: 10.1159/000071219.
22. Marques CM. Tratamento da deficiência de somatropina no adulto. 2016 [consultado 2022 Abr 22]. Disponível em: https://estudogeral.uc.pt/bitstream/10316/33571/1/Trabalho%20Final%20de%206%C2%BA%20Ano%20%20com%20refer%C3%AAncias%20bibliogr%C3%A1ficas.pdf.
23. Rosén T, Wilhelmsen L, Landin-Wilhelmsen K, Lappas G, Bengtsson BA. Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. Eur J Endocrinol.1997; 137:240. doi: 10.1530/eje.0.1370240.
24. McGauley GA. Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand. 1989;356:70. doi: 10.1111/j.1651-2227.1989.tb11249.x.
25. Koranyi J, Svensson J, Götherström G, Sunnerhagen KS, Bengtsson B, Johannsson G. Baseline characteristics and the effects of five years of GH replacement therapy in adults with GH deficiency of childhood or adulthood onset: a comparative, prospective study. The J Clin Endocrinol Metab. 2001;86:4693. doi: 10.1210/jcem.86.10.7896.
26. Tanriverdi F, Kelestimur F. Classical and non-classical causes of GH deficiency in adults. Best Pract Res Clin Endocrinol Metab. 2017;31:3-11. doi: 10.1016/j.beem.2017.02.001.
27. Shalet SM, Toogood A, Rahim A, Bernadette MB. The diagnosis of growth hormone deficiency in children and adults. Endocr Rev. 1998; 19: 203-23. doi: 10.1210/edrv.19.2.0329.
28. Penta L, Cofini M, Lucchetti L, Zenzeri L, Leonardi A, Lanciotti L, et al. Growth Hormone Therapy During the Transition Period: Should We Think About Early Retesting in Patients with Idiopathic and Isolated GH Deficiency? Int J Environ Res Public Health. 2019;16:307. doi: 10.3390/ijerph16030307.
29. Stanley T. Diagnosis of growth hormone deficiency in childhood. Current Opin Endocrinol Diabetes Obes. 2012;19:47-52. doi: 10.1097/MED.0b013e32834ec952.
30. Yuen KC, Tritos NA, Samson SL, Hoffman AR, Katznelson L. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical review: Update on growth hormone stimulation testing and proposed revised cut-point for the glucagon stimulation test in diagnosis of adult growth hormone deficiency. Endocr Pract. 2016; 22:1235-44. doi: 10.4158/EP161407.
31. Boguszewski MC. Growth hormone deficiency and replacement in children. Rev Endocr Metab Disord. 2021; 22:101-8. : 10.1007/s11154-020-09604-2.
32. Tritos NA, Biller BM. Current concepts of the diagnosis of adult growth hormone deficiency. Rev Endocr Metab Disord. 2021;22:109-16. doi: 10.1007/s11154-020-09594-1.
33. Hoeck HC, Vestergaard P, Jakobsen PE, Laurberg P. Test of growth hormone secretion in adults: poor reproducibility of the insulin tolerance test. Eur J Endocrinol. 1995;133:305-12. doi: 10.1530/eje.0.1330305.
34. Yuen KC. Growth Hormone Stimulation Tests in Assessing Adult Growth Hormone Deficiency. Endotext [Internet]. South Dartmouth: MDText.com; 2000 [consultado 2021 Apr 22]. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK395585/.
35. Gasco V, Ferrero A, Bisceglia A, Prencipe N, Cambria V, Bioletto F, et al. The Cut-off Limits of Growth Hormone Response to the Insulin Tolerance Test Related to Body Mass Index for the Diagnosis of Adult Growth Hormone Deficiency. Neuroendocrinology. 2021; 111:442-450. doi: 10.1159/000508103.
36. Piccoli F, Degen L, MacLean C, Peter S, Baselgia L, Larsen F, et al. Pharmacokinetics and pharmacodynamic effects of an oral ghrelin agonist in healthy subjects. J Clin Endocrinol Metab. 2007;92:1814. doi: 10.1210/jc.2006-2160.
37. Yuen KCJ, Llahana S, Miller BS. Adult growth hormone deficiency: clinical advances and approaches to improve adherence. Expert Rev Endocrinol Metab. 2019;14:419-36. doi: 10.1080/17446651.2019.1689119.
38. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML, Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96:1587-1609. doi: 10.1210/jc.2011-0179.
39. Piloto E. Tratamento da Síndrome de Prader-Willi com Somatropina Recombinante: Uma Revisão da Literatura. Rev Port Endocrinol Diabetes Metab. 2017; 12:206-14. doi: 10.1016/j.rpedm.2016.10.011.
40. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS, 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013; 98(6):E1072-87. doi: 10.1210/jc.2012-3888.
41. Comissão Nacional de Normalização da Hormona do Crescimento. Tratamento com somatotropina no adulto. Lisboa: CNNHC; 2020.
42. Kołtowska-Haggstrom M, Hennessy S, Mattsson AF, Monson JP, Kind P. Quality of life assessment of growth hormone deficiency in adults (QoL-AGHDA): comparison of normative reference data for the general population of England and Wales with results for adult hypopituitary patients with growth hormone deficiency. Horm Res. 2005;64:46-54. doi: 10.1159/000087444.
43. Webb SM. Measurements of quality of life in patients with growth hormone deficiency. J Endocrinol Invest. 2008;31:52-5.
44. McKenna SP, Wilburn J, Twiss J, Crawford SR, Hána V, Karbownik-Lewinska M, et al. Adaptation of the QoL-AGHDA scale for adults with growth hormone deficiency in four Slavic languages. Health Qual Life Outcomes. 2011 2;9:60. doi: 10.1186/1477-7525-9-60.
45. Miller BS, Velazquez E, Yuen KCJ. Long-Acting Growth Hormone Preparations - Current Status and Future Considerations. J Clin Endocrinol Metab. 2020; 105:e2121–33. doi: 10.1210/clinem/dgz149.
46. Vance ML. Can growth hormone prevent aging? New Engl J Med. 2003; 348:779-80. doi: 10.1056/NEJMp020186.
47. Bolin K, Sandin R, Koltowska-Häggström M, Loftus J, Prütz C, Jonsson B. The cost-effectiveness of growth hormone replacement therapy

(Genotropin®) in hypopituitary adults in Sweden. Cost Eff Resour Alloc. 2013;11:24. doi: 10.1186/1478-7547-11-24.

48. Johansson JO, Wirén L, Oscarsson J, Bengtsson BA, Gudmundur J. Growth hormone (GH) replacement in GH-deficient adults: a crossover trial comparing the effect on metabolic control, well-being and compliance of three injections per week versus daily injections. Growth Horm IGF Res. 2003; 13: 306-15. doi: 10.1016/S1096-6374(03)00041-8.
49. Yuen K, Bradley M, Boguszewski Cesar L and, Hoffman AR. Usefulness and Potential Pitfalls of Long-Acting Growth Hormone Analogs. Front Endocrinol. 2021; 12: 1664-2392. doi:10.3389/fendo.2021.637209.

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Caso Clínico

Acetazolamida e Diabetes: Um Fator Precipitante de Descompensação Metabólica

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R E S U M O

A cetoacidose diabética consiste numa complicação aguda da diabetes e apresenta uma taxa de mortalidade de cerca de 5%. Dentro dos principais fatores precipitantes, distinguem-se as infeções, a má adesão terapêutica, a doença aguda e os fármacos. Relata-se o desenvolvimento de uma cetoacidose diabética moderada num doente diabético de 71 anos com mau controlo metabólico crónico, sem episódios de descompensação metabólica prévios. Após exclusão dos principais fatores precipitantes desta complicação, apurou-se que o doente tinha iniciado acetazolamida per os 4 dias antes da instalação do quadro como terapêutica de glaucoma neovascular. O presente caso realça o efeito hiperglicemiante da acetazolamida e distingue-a como presumível fator desencadeante de cetoacidose diabética, raramente descrita na literatura como tal. Pretende-se a sensibilização para a prescrição cautelosa deste diurético em doentes diabéticos uma vez que as recomendações do fabricante não alertam para esta situação nesta população específica.

Keywords:
Acetazolamide;
Diabetic Ketoacidosis/chemically induced.

Acetazolamide and Diabetes: A Precipitating Factor of Metabolic Decompensation

A B S T R A C T

Diabetic ketoacidosis is an acute complication of diabetes with a mortality rate of 5%. Infections, medication nonadherence, acute illness and drugs are among the most common precipitating factors. The authors report a diabetic ketoacidosis case in a 71-year-old patient, known to have diabetes with poor metabolic control and without previous metabolic decompensation. After several precipitating factors exclusion, it was found that the patient had started oral acetazolamide as therapy for neovascular glaucoma 4 days before. The present case highlights the hyperglycemic effect of acetazolamide and distinguishes it as a presumptive trigger of diabetic ketoacidosis, rarely described in the literature as a precipitating factor. The authors intend to raise awareness for careful prescription of this diuretic in diabetic patients since the manufacturer's recommendations do not warn of this situation in this specific population.

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Introdução

A cetoacidose diabética (CAD) consiste numa das possíveis complicações metabólicas agudas e graves da diabetes, apresentando uma taxa de mortalidade de cerca de 5%.[1] Dentro dos múltiplos fatores precipitantes de CAD, destacam-se como mais frequentes as intercorrências infeciosas e a má adesão terapêutica. Outros fatores apontados como desencadeantes de CAD são o desenvolvimento de diabetes *de novo* ou de patologia aguda (enfarte agudo do miocárdio, pancreatite aguda, tromboembolismo pulmonar, acidente cerebrovascular, trauma), fármacos, consumo de álcool e drogas de abuso (cocaína).[1-3] Os fármacos que influenciam o metabolismo dos hidratos de carbono poderão precipitar uma CAD, distinguindo-se os seguintes: corticoesteróides, agentes simpaticomiméticos, diuréticos, alguns antipsicóticos, pentamidina e inibidores do co-transportador sódio-glicose 2.[1,4]

Caso Clínico

O presente caso refere-se a um doente de 71 anos, género masculino, com diagnóstico de diabetes tipo 2 determinado em análises de rotina 8 anos antes, sem sintomatologia catabólica associada. Era seguido em consulta de Endocrinologia, estando medicado com antidiabéticos orais - gliclazida 60 mg *id* e metformina+sitagliptina 1000/50 mg *2 id*, que cumpria irregularmente. Destacava-se o mau controlo metabólico crónico - HbA1C 12,7%, associado à presença de complicações microvasculares (retinopatia e neuropatia diabéticas) e macrovasculares (enfarte agudo do miocárdio). Constatava-se ainda ausência de nefropatia diabética, tendo taxa de filtração glomerular estimada de 99 mL/min/1,73 m^2. O doente não tinha registo de eventos de descompensação metabólica aguda prévios. Foi encaminhado ao Serviço de Urgência por quadro de prostração e vómitos com 4 dias de evolução e de agravamento progressivo. A sintomatologia apresentada surgiu após início de toma *per os* de acetozolamida 250 mg para tratamento de glaucoma neovascular, por indicação de Oftalmologia. Não se registava pirexia ou presença de outros sintomas, nomeadamente do foro gastrointestinal, cardiorrespiratório ou neurológico. A gasometria arterial realizada à admissão revelava acidose metabólica - pH 7,21, HCO3 9 mmol/L, *anion gap* aumentado - 23 mEq/L, hiperglicemia - 566 mg/dL, lactatos 1.7 mmol/L; adicionalmente, registava-sepresença de cetose - cetonemia de 3,6 mmol/L e cetonúria. Estes achados eram compatíveis com o diagnóstico de CAD moderada. Analiticamente, apresentava-se com parâmetros de inflamação sistémica discretamente elevados, sem alterações do perfil cardíaco, cirúrgico e urina tipo II; o exame neurológico sumário encontrava-se normal. Excluíram-se causas infeciosas/inflamatórias e omissão terapêutica como fatores precipitantes do evento. O doente iniciou o protocolo hospitalar de correção de CAD com fluidoterapia vigorosa e perfusão de insulina (6 unidades/hora), procedendo-se ao ajuste da perfusão consoante a glicemia capilar. Contudo, o tempo de resolução do quadro foi demorado: decorreram cerca de 65 horas desde a primeira gasometria realizada à admissão até à última compatível com os critérios de resolução estabelecidos pela American Diabetes Association,[1] requerendo-se maiores doses de insulina do que seria expectável. A acetazolamida foi assumida como provável fator desencadeante da CAD, tendo o doente suspendido esta terapêutica. Após estabilização clínica, teve alta e manteve seguimento na consulta de Endocrinologia, não se tendo registado outras complicações metabólicas.

Discussão

A acetazolamida é um diurético com ação inibitória da anídrase carbónica com capacidade de reduzir a secreção de hidrogénio no túbulo renal proximal e aumentar a excreção renal de sódio, potássio, bicarbonato e água; assim, promove bicarbonatúria com consequente alcalinização da urina e diurese. Este fármaco é essencialmente excretado a nível renal.[5] O INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I. P., prevê o uso desta terapêutica nas seguintes situações: glaucoma, retenção anormal de líquidos e epilepsia.[6] Adicionalmente, a agência reguladora Food and Drug Administration indica o seu uso na hipobaropatia (doença da altitude, "mal da montanha"), paralisia periódica e hipertensão intracraniana.[5] Este caso distingue a acetazolamida como presumível fator precipitante do episódio de CAD, após exclusão de outras causas mais frequentes, sendo raramente descrito na literatura como tal. Ao promover a excreção renal de sódio com consequente hipovolémia e bicarbonatúria, aumenta respetivamente o risco de desidratação e de acidose metabólica. Ambos estes fenómenos poderão potenciar e perpetuar o desenvolvimento de CAD.[7] Tendo em conta que os quadros de CAD resolvem habitualmente em 24 horas,[8] o presente caso destaca a acetazolamida como fator precipitante de uma CAD de resolução demorada - cerca de 65 horas, revelando maior necessidade de perfusão de insulina. Reportou-se na literatura que este diurético parece ter um efeito hiperglicemiante; a título de exemplo, um doente diabético tipo 1 com sistema de perfusão subcutânea contínua de insulina teve necessidade de aumento da taxa de perfusão de insulina basal (a 130%) para melhorar o controlo metabólico enquanto realizava terapêutica com acetazolamida per os. Curiosamente, as necessidades de insulina retornaram imediatamente à dose expectável assim que o fármaco foi descontinuado.[9] A diabetes constitui-se como um fator de risco para a toxicidade induzida pela acetazolamida, sendo o mesmo exacerbado perante a coexistência de nefropatia diabética, uma vez que o fármaco é excretado a nível renal. A prescrição deste diurético na área de Oftalmologia é comum como terapêutica de glaucoma, patologia esta que poderá ser particularmente frequente na população diabética.[7,10] Tendo em conta que as recomendações do fabricante não alertam para uma prescrição cautelosa da acetazolamida em doentes diabéticos, visa-se a sensibilização da sua prescrição nesta população específica.

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References / Referências

1. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, et al. Hyperglycemic crises in diabetes. Diabetes Care. 2009; 32:1335-43. doi: 10.2337/dc09-9032.
2. Kitabchi AE, Umpierrez GE, Murphy MB. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. 3rd ed. In: DeFronzo TA, Ferrannini E, KeenH, Zimmet P, editors. International Textbook of Diabetes Mellitus. London: John Wiley & Sons Ltd.; 2004. p. 1101-20.
3. Warner EA, Greene GS, Buchsbaum MS, Cooper DS, Robinson BE. Diabetic Ketoacidosis Associated With Cocaine Use. Arch Intern Med. 1998; 158:1799–802. doi: 10.1001/archinte.158.16.1799.
4. Taylor SI, Blau JE, Rother KI. SGLT2 Inhibitors May Predispose to Ketoacidosis. J Clin Endocrinol Metab. 2015; 100:2849-52. doi: 10.1210/jc.2015-1884.
5. Van Berkel MA, Elefritz JL. Evaluating off-label uses of acetazolamide. Am J Health Syst Pharm. 2018;75:524-31. doi:10.2146/ajhp170279.
6. INFARMED. Resumo das características do medicamento - Acetazolamida. Aprovado em 05-01-2021.Lisboa: INFARMED; 2021.
7. Kerber JM, de Mello JD, Moura KB, da Silva GC, Wawrzeniak IC, Rech TH. Acetazolamide Intoxication in an Elderly Patient with Diabetes and Chronic Renal Failure after Cataract Surgery. Case Rep Crit Care. 2020; 3764972. doi: 10.1155/2020/3764972.
8. Muneer M, Akbar I. Acute Metabolic Emergencies in Diabetes: DKA, HHS and EDKA. Adv Exp Med Biol. 2021;1307:85-114. doi:10.1007/5584_2020_545
9. Miller, SC. Diabetic ketoacidosis and acute mountain sickness: case report and review of treatment options in type 1 diabetes mellitus. Wilderness Environ Med. 2015; 26:185-8. doi: 10.1016/j.wem.2014.09.033.
10. Zhao YX, Chen XW. Diabetes and risk of glaucoma: systematic review and a Meta-analysis of prospective cohort studies. Int J Ophthalmol. 2017;10:1430-5. doi: 10.18240/ijo.2017.09.16.

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Caso Clínico

A Case Series of Follow-ups in COVID-Related Diabetes: Could the Damage in Beta Cells be Recovered?

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A B S T R A C T

SARS-CoV-2 infection may be related to new-onset diabetes and diabetic ketoacidosis (DKA). We describe a long-term follow-up of 3 cases presented in the Emergency Department with DKA and COVID-19. In 2 of them, the clinical course permitted withdrawal of insulin therapy during follow-up. The third case, a more serious one with pulmonary thromboembolism, continued to require bedtime insulin during the follow-up period. Such cases demonstrate that insulin treatment can control glucotoxicity and help beta cells recover after an acute insult such as COVID-19.

Palavras-chave:
Cetoacidose Diabética;
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Uma Série de Casos de Seguimento de Diabetes Relacionada à COVID: Pode o Dano na Célula Beta ser Recuperado?

R E S U M O

A infecção por SARS-CoV-2 pode estar relacionada a diabetes de início recente e cetoacidose diabética (CAD). Descrevemos o seguimento a longo prazo de 3 casos apresentados no Serviço de Urgência com CAD e COVID-19. A evolução clínica em 2 deles permitiu a suspensão de insulinoterapia durante o seguimento. O terceiro caso, mais grave que teve tromboembolismo pulmonar, ainda necessitou de insulina basal ao deitar durante o seguimento. Esses casos demonstram que o tratamento com insulina pode controlar a glicotoxicidade e auxiliar na recuperação das células beta após um insulto agudo como a COVID-19.

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Introduction

The World Health Organization declared the new coronavirus a pandemic at the beginning of 2020. Several cases of diabetes have been recorded as a result of this viral infection. The SARS-CoV-2 virus is thought to increase insulin resistance in peripheral tissues due to cytokines storm, produce beta cell apoptosis resulting in insulinopenia, which predisposes to diabetic ketoacidosis (DKA) even in type 2 diabetes.[1,2] Data and long-term follow-up of these patients are lacking, particularly regarding recovery of beta cell function after virus infection.

Therefore, we aim to describe 3 cases of COVID-related diabetes presenting with DKA, with a longer follow-up than in previous reports.

Case Report

Case 1

A 44-year-old man presented to the Emergency Department (ED) in Abril 2020 referring fever, myalgia, and cough in the past week. He had no comorbidities, no symptom of insulinopenia and no family history of diabetes. On physical examination, he had an oxygen saturation of 80% on room air, a respiratory rate of 40 cpm, and a BMI of 27 kg/m^2. SARS-CoV-2 was confirmed using real-time PCR. Admission test exams revealed hyperglycemia, associated with a high anion gap metabolic acidosis (Table 1) and ketonuria, fulfilling diagnostic criteria for DKA. He received subcutaneous (SC) regular insulin, IV fluids, replacement of electrolytes, oxygen supplementation, and awake prone position; he did not receive corticosteroids since the RECOVERY trial was only published in the end of 2020.[3] Islet cell and glutamic acid decarboxylase antibodies were negative. HbA1c was 12%, with low C peptide value of 0.9 ng/dL (concurrent glucose of 208 mg/dL). His DKA resolved the following day, and he was discharged home after 2 weeks on room air, with SC NPH basal insulin and premeal regular insulin (total daily dose of 0.2 IU/kg). At this time, the diabetes type was still in debate, and type 1B diabetes was one of the differentials proposed.

After one year of follow-up with a low daily insulin dose, his HbA1c decreased to 6.5% with no hypoglycemia. We collected a new C-peptide of 2.4 ng/dL (glucose 189 mg/dL) and switched insulin therapy to metformin 2 g/day due to type 2 diabetes. His HbA1c was maintained in 6.5%.

Case 2

In September 2020, a 44-year-old man presented to the ED with flu-like symptoms for the past week. His mother and sister had a history of type 2 diabetes. He had Down syndrome with no other medical condition. Upon admission, he had an oxygen saturation of 87% on room air, a respiratory rate of 17 cpm, and a BMI of 28 kg/m^2. He also had hyperglycemia associated with a high anion gap metabolic acidosis (Table 1) and ketonuria. Mild DKA was resolved the next day and was managed in the intensive care unit. Real-time PCR for SARS-CoV-2 was positive, his HbA1c was 11.2%, with a C-peptide of 1 ng/dL (glucose 203 mg/dL), and negative type 1A diabetes antibodies (islet cell and glutamic acid decarboxylase antibodies).

This patient did receive dexamethasone for COVID-19 infection. Unfortunately, his condition deteriorated dramatically: he was intubated and submitted to thrombolysis due to an acute pulmonary embolism with severe hypotension.

After nearly 2 months of hospitalization, he was discharged on NPH insulin plus regular insulin of approximately 0.7 IU/kg/day. After 6 months, HbA1c was reduced to 7.7% with no hypoglycemia and a C-peptide of 2.7 ng/dL (glucose 211 mg/dL). We switched to oral therapy and maintained only basal insulin. He achieved good glycemic control (HbA1c 7.1%) with a full dose of metformin, saxagliptin, gliclazide, and bedtime NPH 0.1 IU/kg/day.

Case 3

A 36-year-old man in May 2020 presented to the ED reporting polyuria, polyphagia, altered mental status, and cough in the past week. He had no relevant medical or family history. He was confused, with a Glasgow coma scale of 13, a BMI of 30 kg/m^2, and an oxygen saturation of 96% on room air. Admission exams demonstrated positive real-time PCR for SARS-CoV-2, hyperglycemia, and marked high anion gap metabolic acidosis (Table 1), and ketonuria.

DKA was resolved in 12 hours. He did not receive corticosteroids during hospital stay. The diabetes laboratory investigation revealed a HbA1c of 12.6%, negative islet cell and glutamic acid decarboxylase antibodies, and C-peptide of 4.1 ng/dL (glucose 226 mg/dL). He was initiated on NPH plus regular 0.45 IU/kg/day. After a 6-month follow-up, HbA1c was 6.1% (with no hypoglycemia, using only NPH 0.2 IU/kg/day), and C-peptide was

Table 1. Clinical and laboratory tests performed on patients during admission and follow-up.

	Case 1	Case 2	Case 3	Reference
Arterial pH	7.26	7.25	7	7.35-7.45
Bicarbonate (mmol/L)	15	15.4	7	20-24
pCO2 (mmHg)	33	32	29	35-45
Anion gap	22	17	24	8-12
Glucose (mg/dL)	307	460	980	<200
DKA classification	Mild	Mild	Severe	-
Arterial lactate (mg/dL)	15	8	7	4.5-14.4
Islet cells and glutamic acid decarboxylase antibodies	Negative	Negative	Negative	-
Initial C-peptide (ng/dL)*	0.9	1	4.1	1.1-4.4
Follow-up C-peptide (ng/dL)*	2.4	2.7	4	1.1-4.4
Admission HbA1c (%)	12	11.2	12.6	4%-5.6%
HbA1c after switch of diabetes drug therapy (%)	6.5	7.1	5.9	4%-5.6%
Total daily insulin dose prescribed after discharge (IU/kg/day)	0.2	0.7	0.45	-
Total daily insulin dose during follow-up (IU/kg/day)	-	0.1	-	-

* The glucose level was greater than 150 mg/dL at the time of sample collection.

4 ng/dL (glucose 177 mg/dL). Insulin therapy was withdrawn and the patient received a full dose of metformin with satisfactory glycemic control (HbA1c 5.9%).

Unfortunately, the Public Health System in Brazil does not provide GLP1 analogs, which would be an excellent choice for both diabetes and weight control. Moreover, our ED does not have capillary ketonemia and the DKA diagnosis in all cases was based on ketonuria. Other causes of high anion gap acidosis were ruled out for all presented cases: there was no history or clinical signs of exogenous intoxication, lactate was only mildly elevated in case 01 (Table 1) – probably due to the acute respiratory infection, and none of the patients had chronic kidney disease.

Discussion

Epidemiology studies comparing pre-pandemic versus first and second waves in COVID highlight an increase in admission to the ED for DKA, especially in type 2 diabetes.[4]

The mechanism responsible for hyperglycemia and DKA in COVID-19 is not well known and it is probably multifactorial. Theories include a possible previous undiagnosed diabetes, which could be triggered by lifestyle changes during the pandemic period (weight gain, self-isolation, decreased physical activity, and high-calorie diet).[5]

Stress-related hyperglycemia is another factor that influences glycemic levels. Even though hyperglycemia is not rare in acute ill-hospitalized patients, some evidence proposes that new-onset diabetes seems more prevalent due to COVID-19 rather than another acute event.[6]

Impairment in pancreatic function and insulin resistance may be caused by cytokine storm, in situ thrombosis leading to pancreatic cell ischemia, and direct viral replication.[7] The SARS-CoV-2 binds to ACE2 receptors expressed in the pancreatic beta cells, enters the cell for replication, diminishes pancreatic insulin levels, and can directly induce beta cell apoptosis.[1,8] All of these factors can lead to insulinopenia and increase the risk of DKA.

After the publication of the RECOVERY trial, corticosteroids were used to decrease mortality in COVID-19.[3] Besides those complex mechanisms that induce hyperglycemia, the use of steroids became another risk factor as it delays the recovery of beta cell function and increases insulin resistance.[5]

The real impact on the future secretion of insulin is unknown, although cases 01 and 03 show that beta cells can be preserved, especially following intensive treatment to stop glucotoxicity. Interestingly, Weng *et al* demonstrated in 2008 that intensive insulin treatment in newly diagnosed type 2 diabetes could maintain beta cell function and achieve diabetes remission even after one year of insulin therapy discontinuation.[9]

A larger retrospective study with 1902 subjects with COVID-19 showed that 77 (13%) had newly diagnosed diabetes. Compared to the patients with pre-existing diabetes, they had lower glycemic values, were younger, had longer hospital stay and intensive care unit admission, and had higher inflammatory markers. Although 25 (39.1%) of them were discharged on insulin, after one year of follow-up 26 (40.6%) regressed to normoglycemia or pre-diabetes.[10] Authors suggested the term "newly diagnosed diabetes" over "new-onset diabetes", as it is unclear in many cases whether the diabetes is truly new-onset or merely newly recognized. In fact, in their study, almost 70% of the newly diagnosed diabetes group had HbA1c >6.5% at admission. Like our patients, HbA1c levels indicate that they most likely had undiagnosed type 2 diabetes prior to COVID-19 diagnosis.

Post-COVID syndrome or long COVID is defined by signs or symptoms that can be reminiscent after 12 weeks of the viral disease. Although causality cannot be established, a relationship in diabetes development post-COVID has been described.[11] Wander *et al*, in a retrospective cohort, found a 2.56-fold increase in diabetes incidence in veteran American men after viral infection.[12] A matched pair analysis of a German healthcare database also identified an increased incidence rate ratio of 1.28 in type 2 diabetes in infected patients.[13] Type 1 diabetes, on the other hand, did not appear to have increased in incidence.[14]

The SARS-CoV-2 infection intensifies the risks and accelerates the manifestation of diabetes among individuals at high risk of diabetes. According to Xie *et al*, even people at low risk of diabetes revealed an increased risk after COVID-19, compared to the control group. Therefore, they concluded that post-COVID care should include routine screening and management of diabetes.[15]

In conclusion, the purpose of these cases is to describe a longer follow-up in patients with COVID-related diabetes. Early insulin therapy should be considered since apparently there might be a chance to recover beta cell function. More studies are needed concerning longer follow-up after COVID-19 to investigate diabetes in this population.

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MAMS: Conceptualization, data collection, writing original draft, and final approval.
LPL: Writing original draft, review and final approval.
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References / Referências

1. Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: Causality or coincidence? A report of three cases. J Med Virol. 2021; 93: 1150-53.
2. de Sá-Ferreira CO, da Costa CH, Guimarães JC, Sampaio NS, Silva LM, de Mascarenhas LP, et al. Diabetic ketoacidosis and COVID-19: what have we learned so far? Am J Physiol Endocrinol Metab. 2022; 322: E44-E53.
3. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384: 693-704.
4. Misra S, Barron E, Vamos E, Thomas S, Dhatariya K, Kar P, et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. Lancet Diabetes Endocrinol. 2021; 9: 671-80.
5. Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, Hyperglycemia, and New-Onset Diabetes. Diabetes Care. 2021; 44: 2645-55.
6. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Obes Metab. 2021; 23: 870-74.
7. Qadir MMF, Bhondeley M, Beatty W, Gaupp DD, Doyle-Meyers LA, Fischer T, et al. SARS-CoV-2 infection of the pancreas promotes thrombofibrosis and is associated with new-onset diabetes. JCI Insight. 2021; 6: e151551.
8. Wu CT, Lidsky PV, Xiao Y, Lee IT, Cheng R, Nakayama T, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. Cell Metab. 2021; 33: 1565-76
9. Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet. 2008; 371: 1753-60.
10. Cromer SJ, Colling C, Schatoff D, Leary M, Stamou MI, Selen DJ, et al. Newly diagnosed diabetes vs. pre-existing diabetes upon admission for COVID-19: Associated factors, short-term outcomes, and long-term glycemic phenotypes. J Diabetes Complications. 2022; 36: 108145.
11. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021; 372:n693.
12. Wander PL, Lowy E, Beste LA, Tulloch-Palomino L, Korpak A, Peterson AC, et al. The incidence of diabetes among 2,777,768 veterans with and without recent SARS-CoV-2 infection. Diabetes Care. 2022; 45: 782-88.
13. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. Diabetologia. 2022; 65: 949-54.
14. Kamrath C, Rosenbauer J, Tittel SR, Warncke K, Hirtz R, Denzer C, Dost A, Neu A, Pacaud D, Holl RW. Frequency of autoantibody-negative type 1 diabetes in children, adolescents, and young adults during the first wave of the COVID-19 pandemic in Germany. Diabetes Care. 2021; 44: 1540-46.
15. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. Lancet Diabetes Endocrinol. 2022; 10: 311-21.

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Caso Clínico

Diabetic Muscle Infarction in a 45-Year-Old Male

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Doenças Musculares;
Enfarte;
Ressonância Magnética.

A B S T R A C T

Diabetic muscle infarction is a rare complication of diabetes mellitus, affecting patients with long-standing disease and poor glycemic control.
A 45-year-old male, with history of longstanding (15 years) type 2 diabetes, presented to the Emergency room with bilateral muscle leg pain and gait impairment. Neurological examination showed no neurological focal signs or impaired muscle strength.
Urgent ultrasound examination of both thighs was compatible with ischemic muscle changes in the lateral left and medial right thigh muscles. Thigh magnetic resonance revealed bilateral infarction of the vastus medialis and left vastus lateralis muscles. The patient was started on anti-inflammatory drugs and low-dose aspirin. Pain resolved two weeks after admission and there was no gait limitation at discharge.
Current data is limited on which therapeutic and management approaches should be indicated and future studies should further investigate the role of anti-inflammatory drugs in diabetic muscle infarction, as well as the impact of glycemic control on recurrence rates.

Enfarte Muscular Diabético num Homem de 45 Anos de Idade

R E S U M O

O enfarte muscular diabético é uma complicação rara da diabetes, em casos de doença prolongada e mal controlada.
Um homem de 45 anos, com história de diabetes tipo 2 de longa data (15 anos de evolução), apresentou-se no serviço de urgência com dor muscular bilateral nas pernas e comprometimento da marcha. O exame neurológico não mostrou sinais neurológicos focais ou diminuição da força muscular.
A ecografia das coxas foi compatível com alterações musculares isquémicas. A ressonância magnética das coxas revelou enfarte bilateral dos músculos vasto medial e vasto lateral esquerdo. Foi iniciado tratamento com anti-inflamatórios e aspirina em baixa dose. A dor resolveu em duas semanas após a admissão e não havia limitação da marcha à alta.
Os dados atuais são limitados sobre quais abordagens terapêuticas mais indicadas e estudos futuros devem investigar melhor o papel dos anti-inflamatórios no enfarte muscular diabético, bem como o impacto do controlo metabólico nas taxas de recorrência.

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Introduction

Despite not being the most frequent constellation of symptoms at the emergency department, lower limb pain and gait impairment are frequent complains that lead to an urgent consultation.

These symptoms may have multiple causes, from systemic infection and medication toxicity to auto-immune diseases, polyneuropathy and inflammatory myopathies. Localized lower limb myalgias have, however, a narrower list of differential diagnosis and diabetic muscle infarction, although rare, must be thought of if the presentation is acute or subacute and there is past history of longstanding and poorly controlled diabetes mellitus.

Existing evidence on diabetic muscle infarction or spontaneous diabetic myonecrosis is based on case reports and analyses of the findings described in each of them, so its prevalence is difficult to determine. This condition was first described in 1965, and since then less than 200 cases have been reported.[1] It is considered to be a complication of diabetes mellitus although there is no consensus on the pathogenic mechanisms responsible.[2] Microangiopathic changes, vasculitis or ischemia-reperfusion injury are some of the mechanisms proposed.[2-4] Clinically, diabetic muscle infarction is characterized by acute or subacute pain, swelling and tenderness of thigh or calf, unrelated to trauma or exercise and evolving over days to weeks. It occurs in both type 1 and type 2 diabetes, and most of the patients have other associated microvascular complications.[2,5]

In a 2015 systematic review, mean age at presentation was 45 years-old and bilateral presentation occurred in about eight percent of the cases analysed.[2] Routine laboratory tests are often unrevealing, with normal to mildly elevated leukocyte counts, CK levels and erythrocyte sedimentation rates.[2] Measurements of glycated hemoglobin are usually high (mean 9.3% in the 2015 systematic review).[2] Diagnosis is made combining clinical data and imaging results. Ultrasound and magnetic resonance imaging (MRI) are useful diagnostic imaging options, with MRI yielding the most specific results.[2,6,7] Muscle biopsy is reserved for when the diagnosis remains unclear despite clinical, laboratory and imaging data.[8]

Management options include bed rest, symptomatic relief, non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin and glycemic control as these strategies appear to be associated with the shortest recovery times and lower recurrence rates, although limited data exist on these approaches.[2]

Mean time to symptom resolution ranges from 28.5 to 81.6 days, depending on treatment option, with physiotherapy and surgery being associated with longer recovery times.[2,3] Recurrence rates reported are high, ranging from 10% to 50%. Treatment with NSAIDs has been found to relate to a lower recurrence risk (10%).

Case Report

We describe the case of a 45-year-old male with past medical history of ill-controlled type 2 diabetes mellitus (with 15 years of evolution) who presented to our ER with bilateral thigh myalgias and gait disturbance. These symptoms had started one week before and evolved to unbearable and constant muscle pain on both thighs, partially ameliorated when standing. There was no history of trauma or intense exercise and the patient denied pain in any other muscle group. Diabetes mellitus diagnosis was made when he was 30 years old and, despite no specialist follow-up, he had no diagnosed micro- or macrovascular complications. Current patient medication included oral anti-diabetics (metformin 1000 mg qd + vildagliptin 50 mg qd and gliclazide 30 mg qd), insulin basal-bolus scheme (although the patient admitted to a weak compliance with his insulin administration scheme), sinvastatin 20 mg qd and sertraline 50 mg qd. None of these drugs had been introduced or changed in the last year.

Neurological examination had no evidence of neurological focal signs, namely no motor or sensitive deficits. Thigh movements showed normal muscle strength bilaterally. Bilateral thigh active or passive movement and muscle palpation were extremely painful. There was no apparent muscle swelling or hypertrophy nor associated skin changes. Gait was difficult due to pain, with incapacity to walking more than 2-3 consecutive steps without help, but there was no ataxia. Physical examination was otherwise unrevealing.

The patient had a high glucose level at admission (>300 mg/dL), was hemodynamically stable and afebrile. Blood tests revealed mildly elevated CK levels (322 U/L), no leukocytosis and normal D-dimers, erythrocyte sedimentation rate and C-reactive protein values. Blood cultures were obtained in order to exclude infectious muscle necrosis.

Thigh ultrasound showed increased thickness and echogenicity of thigh skin bilaterally with associated muscle hyper-echogenicity. Ultrasonographic structure was heterogeneous in the lateral left and medial right thigh regions, with hypoechoic regions interspersed, suggesting muscle infarction in these topographies. Venous walls appeared thickened, but there were no signs of venous thrombosis. Arterial Doppler ultrasound showed no relevant stenotic or occlusive lesions on both legs. These findings were further characterized by thigh MRI which revealed subcutaneous edema on both thighs, and hyperintense signal of the right vastus medialis and left vastus lateralis muscles on T2- weighted images. These muscles appeared hypointense on T1-weighted images with interspersed areas of T1 hyperintensity, suggesting hemorrhagic transformation areas inside infarcted muscles (Fig. 1).

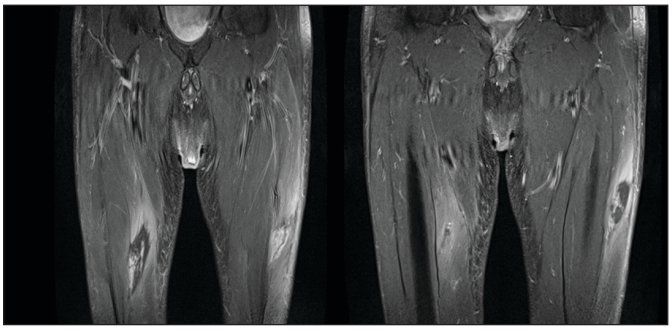

Figure 1. Bilateral diabetic muscle infarction.
Thigh MRI hyperintense signal of the right vastus medialis and left vastus lateralis muscles on T2- weighted images.

The patient was admitted and started on NSAIDs (ibuprofen 400 mg 3 id) and low-dose aspirin (100 mg id). Glycemic control was achieved during hospital stay mainly due to better compliance to insulin therapy. Further laboratory tests revealed a glycated hemoglobin of 14%. Serum creatinine levels were 1.49 mg/dL at admission but normalized during hospital stay. Auto-immunity markers, including antinuclear antibody (ANA) and anti-neutrophil cytoplasmic antibody (ANCA) status, and myopathy antigen antibodies were negative, as were the blood cultures. Coagulation

studies showed no abnormalities. No signs of compartment syndrome or other complications were detected during hospital stay.

Bed rest was preferred is the first week, but mild physical activity was encouraged as soon as severe pain subsided. Rest and movement associated muscle pain resolved in two weeks after admission. At discharge from in-hospital care there was no gait limitation. Mild thigh tenderness persisted. Aspirin was maintained and follow-up consultations scheduled for vigilance of glycemic control, other vascular risk factors and recurrence signs.

Conclusion

Diabetic muscle infarction is a rare but potentially serious complication of diabetes mellitus, affecting mainly young adults with longstanding and poorly controlled diabetes. Symptoms and signs may be interpreted in the context of other (more frequent) causes of leg pain, and this may result in delays in diagnosis and treatment or lead to the use of invasive and unnecessary diagnostic tests. Therefore, a high clinical suspicion is the key to identify this condition, and to correctly choose complementary diagnostic techniques and initiate treatment shortly after presentation. Current data is limited on which therapeutic and management approaches should be indicated, although existing evidence supports the use of NSAIDs and aspirin (providing that there are no contra-indications) as these strategies seem to be associated with shorter recovery times. Rigorous glycemic control should be targeted in order to prevent, not only the more common micro- and macrovascular complications of diabetes, but also recurrence of diabetic muscle infarction.

In this clinical case, early recognition of diabetic muscle infarction allowed for early treatment and risk factor control, which resulted in a relatively short recovery time. Ultrasound and MRI were crucial for confirming diagnosis. Treatment strategy chosen (with aspirin, NSAIDs and rest) was based on the existing evidence from case reports and small case series and absence of contra-indications for the use of these medications. Future studies should, however, further investigate the role of NSAIDs and other therapeutic approaches in diabetic muscle infarction, as well as the impact of these strategies and glycemic control on recurrence rates and prognosis of this condition.

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References / Referências

1. Angervall L, Stener B. Tumoriform focal muscular degeneration in two diabetic patients. Diabetologia. 1965;1:39-42. doi:10.1007/BF01338714
2. Horton WB, Taylor JS, Ragland TJ, Subauste AR. Diabetic muscle infarction: A systematic review. BMJ Open Diabetes Res Care. 2015;3:e000082. doi:10.1136/bmjdrc-2015-000082
3. Chester CS, Banker BQ. Focal infarction of muscle in diabetics. Diabetes Care. 1986;9:623-30. doi:10.2337/diacare.9.6.623
4. Trujillo-Santos AJ. Diabetic muscle infarction: An underdiagnosed complication of long-standing diabetes. Diabetes Care. 2003;26:211-5. doi:10.2337/diacare.26.1.211
5. Lentine KL, Guest SS. Diabetic muscle infarction in end-stage renal disease. Nephrol Dial Transplant. 2004;19:664-9. doi:10.1093/ndt/gfg580
6. Chason DP, Fleckenstein JL, Burns DK, Rojas G. Diabetic muscle infarction: Radiologic evaluation. Skeletal Radiol.1996;25:127-32. doi:10.1007/s002560050048
7. Huang BK, Monu JUV, Doumanian J. Diabetic myopathy: MRI patterns and current trends. Am J Roentgenol. 2010;195:198-204. doi:10.2214/AJR.09.2494
8. Kapur S, Brunet JA, McKendry RJ. Diabetic muscle infarction: case report and review. J Rheumatol. 2004;31:190-4.

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Caso Clínico

Insulinoma Misdiagnosed as Factitious Hypoglycemia

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A B S T R A C T

Hypoglycemia is an important cause of referral to endocrinologists. We report a case of 34-year-old female presenting with Whipple's triad. The blood test documented hyperinsulinemic hypoglycemia and the presence of glibenclamide. Blood tests were repeated, confirming the results. Considering these laboratory findings, factitious hypoglycemia was suspected and the patient was referred to a psychiatry clinic. However, following further investigation, a pancreatic neuroendocrine tumor was diagnosed and submitted to surgical resection. At this point two highly unlikely scenarios remained: either the patient had a simultaneous diagnosis of a neuroendocrine tumor and factitious hypoglycemia or the glibenclamide result was a false positive due to a serum interference. In order to clarify the situation further investigation was performed and the interference hypothesis was confirmed. This case shows that a diagnosis of factitious hypoglycemia should not be categorically assumed, even when in the presence of a positive measurement of secretagogues in blood tests.

Insulinoma Diagnosticado como Hipoglicemia Factícia

R E S U M O

A hipoglicemia é uma das causas de referenciação à consulta de Endocrinologia. Apresentamos o caso de uma doente de 34 anos encaminhada por sintomatologia compatível com tríade de Whipple. A avaliação analítica documentou hipoglicemia hiperinsulinémica e, na mesma amostra, doseamento positivo de glibenclamida. Foi realizada uma nova colheita e confirmados os resultados. Tendo em conta a avaliação analítica, foi assumido o diagnóstico de hipoglicemia factícia e a doente foi encaminhada à consulta de Psiquiatria. Contudo, após investigação adicional, foi diagnosticado um tumor neuroendócrino pancreático. Nesta fase, colocaram-se duas hipóteses: tratar-se de um tumor neuroendócrino não funcionante e apresentar, concomitantemente, hipoglicemia facticia, ou tratar-se de um insulinoma e o doseamento de glibenclamida ter sido um falso positivo. Foi realizada investigação adicional e confirmou-se a segunda hipótese. Com este caso, salientamos a importância de considerar a presença interferentes, independentemente do método laboratorial, e não assumir categoricamente o diagnóstico de hipoglicemia factícia.

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Introduction

Hypoglycemia is an uncommon clinical issue in patients not undergoing treatment for diabetes mellitus.[1] The symptoms of hypoglycemia include autonomic symptoms, such as tremor, diaphoresis, hunger, and palpitations, and neuroglycopenic symptoms, such as dizziness, weakness, drowsiness, confusion and altered mental status. The evaluation and management of hypoglycemia is only recommended in patients in whom Whipple's triad is documented.[2] Whipple's triad consists of symptoms and/or signs of hypoglycemia, low plasma glucose concentration and relief of symptoms following the administration of glucose. In these patients a detailed clinical history, physical examination and laboratory evaluation are fundamental. When the cause of the hypoglycemic disorder is not obvious, the laboratorial evaluation should include the measurement of plasma glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate concentrations and screening for oral hypoglycemic agents (sulfonylureas and meglitinides). The blood samples should be collected during an episode of spontaneous hypoglycemia. Insulin antibodies should also be measured, since autoimmune hypoglycemia is a differential diagnosis of hyperinsulinemic hypoglycemia.[3] When a spontaneous hypoglycemic episode cannot be observed, a provocative test of 72-hour fast should be performed. If the hypoglycemia typically occurs in the postprandial period, a mixed-meal test might be the preferred provocative procedure.[1] By observing the presence of symptoms and signs of hypoglycemia and performing the above laboratory evaluation, it is usually possible to distinguish between the several causes of hypoglycemia.

Case Report

Female patient, 34-year-old, with no relevant personal history. The patient reported only an aunt with type 2 diabetes mellitus and one cousin with type 1 diabetes mellitus, with no other relevant familial history. The patient was referred to our endocrinology clinic due to recurrent episodes of diaphoresis, tremor, weakness, hunger, and blurred vision associated with hypoglycemia resolving after eating and achieving normal blood glucose levels, configuring Whipple's triad. The patient's weight remained stable, and no other symptoms were reported. These symptoms began eight months before and were becoming more frequent and incapacitating. At first, hypoglycemic episodes occurred predominantly during the night period, after long fasting periods. However, in the previous five months these symptoms started to occur in the postprandial period as well. The patient was evaluated by a general practitioner and was medicated with metformin, which the patient stopped taking after two weeks due to worsening symptoms. Three months later the patient was evaluated in our endocrinology clinic for the first time. A laboratorial evaluation of hypoglycemia was requested. The blood tests were collected after a fasting night period, revealing glycemia of 31 mg/dL, insulin 14.0 uUI/mL (reference range 3.0-25.0), pro-insulin 13.3 pmol/L (reference range 0.7-4.3), C peptide 2.9 ng/mL (reference range 0.8-3.9), insulin antibodies of 6.0% (negative < 8.2). In the same blood sample, the measurement of circulating oral hypoglycemic agents revealed detectable levels of glibenclamide of 0.15 ug/mL (reference range 0.03-0.20). However, the patient denied taking any herbal supplements or medication, except for metformin, which she had stopped taking 4 months prior. Due to these findings, we decided to repeat the blood tests that revealed, once again, detectable levels of glibenclamide (0.04 ug/mL, reference range 0.03-0.20), glycemia 46 mg/dL and high levels of insulin, pro-insulin and C peptide. At this point the diagnosis of factitious hypoglycemia induced by oral hypoglycemic agents was considered the most likely hypothesis, and the patient was referred to the psychiatry department. The psychiatric evaluation excluded Munchausen syndrome, personality disorders and any other psychiatric disorder that could justify a case of factitious hypoglycemia. Since the symptoms persisted, the patient asked for a second evaluation at a different medical clinic. An abdominal magnetic resonance was performed, showing a pancreatic lesion in the body/tail transition, with a larger axis of 16 mm. Cytology by echo-endoscopy was performed and the results were suggestive of a neuroendocrine tumor. The patient was submitted to distal pancreatectomy and splenectomy, with no intercurrences. The histological examination confirmed the diagnosis of a well differentiated G2 neuroendocrine tumor, with 20 mm of larger axis, 3 mitoses per 50 high power fields, Ki67 10%, with no lymph nodes metastasis detected in the 22 nodes that were excised. There was a complete resolution of symptoms after the surgery. The C peptide, plasma insulin, proinsulin and serum glucose levels returned to normal. Plasmatic glibenclamide, however, remained detectable (0.70 ug/mL). In order to confirm the presence of an interfering substance, we opted to collect a blood sample at morning for measurement of serum glibenclamide concentration, followed by an urine sample 8 hours later in order to test for glibenclamide metabolites. The blood test was positive for glibenclamide (0.59 ug/mL) but no metabolites were identified in the urine sample. Thus, the diagnosis of an insulinoma was assumed. In this case, there was no familial history of endocrine tumors and at this point patient does not present any evidence of other tumors associated to MEN1 syndrome.

Discussion

An hypoglycemic disorder is established by the presence of Whipple's triad, characterized by the presence of symptoms and signs consistent with hypoglycemia, a documented low plasma glucose concentration and resolution of symptoms after glucose administration and correction of hypoglycemia.[2,4] Once the presence of a hypoglycemic disorder is confirmed, it is important to establish the etiology. In this case, the initial laboratory evaluation was performed after an overnight fast period, documenting a case of hyperinsulinemic hypoglycemia. Adult-age onset hyperinsulinemic hypoglycemia may be caused by an insulinoma, autoimmune hypoglycemia syndrome, factitious hypoglycemia due to exogenous administration of insulin or secretagogues, pancreatogenous hypoglycemia syndrome, related to bariatric surgery, or by a paraneoplastic syndrome due to tumors of mesenchymal or epithelial origin.[5,6] Factitious hypoglycemia resulting from exogenous insulin administration is promptly distinguished from hypoglycemia resulting from endogenous hyperinsulinism by an inappropriately high insulin level in presence of suppressed C-peptide and proinsulin levels.[7] On the other hand, insulinomas and insulin secretagogues, like sulfonylureas and meglitinides, present with increased levels of plasma insulin, C peptide and proinsulin.[4] The only way to differentiate between insulinoma and secretagogues induced hypoglycemia is by detecting the drug in the blood or urine tests.[4] In presence of detectable levels of an oral hypoglycemic agent, accordingly with literature, no further investigation is needed. In the reported case, glibenclamide was detected in two different blood samples, using high performance liquid chromatography (HPLC). Thus, facing these results we suspected of factitious hypoglycemia and requested observation by psychiatry

department. Factitious hypoglycemia may be a potential differential diagnosis in patients who work in the medical field, who are in close contact with diabetic individuals, and those with underlying psychiatric disorders.[4] During psychiatric evaluation, the observation was suggestive of anxiety disorder with no associated signs of psychopathology, including Munchausen syndrome, that could justify a factitious hypoglycemia. The definitive diagnosis by histological examination was a pancreatic neuroendocrine tumor. However, the term "insulinoma" is only applied if the symptoms and laboratory data are consistent with excessive production of endogenous insulin. Thus, in this case we could hypothesize the presence of a non-functioning neuroendocrine tumor associated with factitious hypoglycemia or, in the other hand, that the glibenclamide detection might be a false positive and the neuroendocrine tumor might be an insulinoma. HPLC is a very accurate and precise method that separates and identifies various compounds in a mixture according to their retention time (tR), by comparing each peak's tR with that of injected reference standards. However, like any other laboratory method, HPLC also has its pitfalls. Although rare, it's possible that two molecules present the same tR (molecules with very similar structures, eg). In this case we suspect that the patient's serum had an interferent substance with the same tR as glibenclamide, which was responsible for a false positive result. To confirm this scenario a blood sample was collected for serum measurement of glibenclamide, and a urinary sample 8 hours later, the time required for the metabolization and excretion of glibenclamide and its metabolites. The blood sample was once again positive for glibenclamide by HPLC method but the urine sample was negative for this drug and its metabolites, using the same laboratorial method (HPLC). These results support the serum interference hypothesis.

We could not conclude which substance was causing this result, since the patient denied taking any medication, herbal preparations or other supplements. To our knowledge, there are no common drugs or substances reported in literature with the same tR as glibenclamide, up to this moment. In this particular case, if the first laboratorial result was considered reliable, and no further investigation was ordered, we would have missed a potentially life-threatening diagnosis of insulinoma, in spite of acting in accordance to international guidelines. We are reporting this case of an insulinoma, as a particularly bewildering differential diagnosis of a hyperinsulinemic hypoglycemia. Even in presence of positive measurement of secretagogues in blood tests, we cannot categorically assume factitious hyperinsulinemic hypoglycemia as the definitive diagnosis, since every laboratorial exam may have potential interfering substances.

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References / Referências

1. Service FJ. Hypoglycemic disorders. N Engl J Med. 1995;332:1144-52. doi: 10.1056/NEJM199504273321707.
2. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94:709-28. doi: 10.1210/jc.2008-1410.
3. Davi MV, Pia A, Guarnotta V, Pizza G, Colao A, Faggiano A; NIKE Group. The treatment of hyperinsulinemic hypoglycaemia in adults: an update. J Endocrinol Invest. 2017;40:9-20. doi: 10.1007/s40618-016-0536-3.
4. Awad DH, Gokarakonda SB, Ilahi M. Factitious Hypoglycemia. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022.
5. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. Lancet Diabetes Endocrinol. 2017;5:729-42. doi: 10.1016/S2213-8587(16)30323-0.
6. Kittah NE, Vella A. Management of endocrine disease: Pathogenesisand management of hypoglycemia. Eur J Endocrinol. 2017;177:R37-R47. doi:10.1530/EJE-16-1062.
7. Griffiths MJ, Gama R. Adult spontaneous hypoglycaemia. Hosp Med. 2005;66:277-83. doi: 10.12968/hmed.2005.66.5.
8. Rajendran S, Philip B, Gopinath R, Suresh B. RPHPLC method forthe estimation of glibenclamide in human serum. Indian J Pharm Sci. 2007;69: 796–9. doi: 10.4103/0250-474X.39436.

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Caso Clínico

An Exuberant Manifestation of Subacute Thyroiditis SARS-CoV-2-Related

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A B S T R A C T

A variety of clinical manifestations attributable to SARS-CoV-2 has been described, including subacute thyroiditis (SAT). Here we describe an atypical case of SAT SARS-CoV-2-related.
A 34-year-old previously healthy woman presented to the emergency room complaining of intense cervical pain, non-responsive to ibuprofen, 12 days after being diagnosed with infection with SARS-CoV-2. Clinical, laboratory, and imaging features were compatible with SAT. She was discharged with prednisolone 40 mg/day. After reducing prednisolone, cervical pain recurred, and she experienced intense thyrotoxicosis symptoms and fever. Due to persistent high fever and absence of improvements with treatment, the patient was hospitalized. Imaging did not show abscesses. Clinical improvement was seen when prednisolone was increased to 60 mg/day. Ten weeks after the initial symptoms, she was asymptomatic, with normal free T3 and T4.
SAT is a possible complication of SARS-CoV-2 infection. Clinicians should be alerted to this diagnosis and to potentially refractoriness to standard treatment, and more exuberant and long-lasting forms of SAT, even in the presence of mild forms of COVID-19.

Uma Manifestação Exuberante de Tiroidite Subaguda Associada a Infeção por SARS-CoV-2

R E S U M O

Têm sido descritas inúmeras manifestações clínicas atribuídas ao SARS-CoV-2, incluindo tiroidite subaguda (TSA). Descrevemos um caso atípico de TSA associada à infeção por SARS-CoV-2.
Mulher de 34 anos, previamente saudável, recorreu ao serviço de urgência por dor cervical intensa, não responsiva a ibuprofeno, 12 dias após infeção por SARS-CoV-2. Quadro clínico, analítico e imagiológico compatível com TSA. Alta medicada com prednisolona 40 mg/dia. Após redução da dose, teve agravamento das queixas álgicas, febre e sintomatologia acentuada de tireotoxicose. Por ausência de melhoria com tratamento sintomático e persistência da febre, decidido internamento. Sem evidência de abcesso nos exames de imagem. Melhoria após aumento da prednisolona para 60 mg/dia. Dez semanas após os sintomas iniciais, a doente ficou assintomática, com frações livres dentro dos valores de referência.
A TSA é uma possível complicação da infeção por SARS-CoV-2. Os clínicos devem estar alerta para este diagnóstico e para a possibilidade de refratariedade ao tratamento convencional e de manifestações mais exuberantes e prolongadas de TSA, mesmo em casos de sintomas ligeiros de COVID-19.

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Introduction

The highly contagious disease called coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has rapidly spread around the world, and it is associated with important morbimortality.[1,2] Although most patients with COVID-19 have respiratory tract symptoms, a wide range of clinical manifestations attributable to this infection have been described, such as neurological,[3] gastrointestinal4, and endocrinological[5] complications. One of the endocrine organs commonly affected is the thyroid gland, leading to various disorders, including subacute thyroiditis (SAT).[5,6]

SAT is a self-limited inflammatory thyroid disease, and it is a relatively infrequent cause of thyrotoxicosis.[7,8] Evidence supports a viral or postviral origin for this disease, being often preceded by an upper respiratory tract infection. Many viruses have been reported as potentially causative agents, such as influenza, adenovirus, or coxsackie.[9,10]

We describe a case of COVID-19-related SAT associated with exuberant manifestations, with high fever, persistent intense cervical pain, and the need for high doses of prednisolone for a prolonged period.

Case Report

On 8th December 2020, a 34-year-old caucasian woman, with no relevant past medical history, developed ageusia, anosmia, myalgia, and subfebrile temperature (37.5-37.8ºC). On 11st December, a real-time reverse transcription-polymerase chain reaction of a nasopharyngeal swab was performed confirming infection by SARS-CoV-2. No specific treatment was necessary, and the patient was expected to recover completely. Nonetheless, five days after the diagnosis of COVID-19 and eight days after the initial onset of symptoms, the patient reported severe permanent pain in the anterior cervical region, with irradiation to the retroauricular region, predominantly on the right side. She self-medicated with ibuprofen (600 mg thrice daily), with a slight improvement of the pain. After an initial improvement, five days later, she started experiencing severe cervical pain and *de novo* subfebrile temperature (~37.5ºC) refractive to ibuprofen. Due to that, two days later, after seven days taking the non-steroidal anti-inflammatory drug and 12 days after the diagnosis of COVID-19, she presented to the emergency department (ED). She had also lost 4 kg unintentionally during that week. She denied any upper respiratory symptoms. Physical examination was unremarkable except for an enlarged and markedly painful thyroid gland at palpation.

Laboratory tests were requested (Fig. 1) showing a low TSH [0.127 uUI/mL; reference range (RR) 0.55–4.78], high free triiodothyronine (FT3) (6.05 pg/mL; RR 2.3-4.2), high free thyroxine (FT4) (2.26ng/dL; RR 0.89-1.76), high C-reactive protein (CRP) (206 mg/L; RR <5.0), an elevated white blood cell count (12.7×10^3/uL; RR 4.0-11.0) with high neutrophil percentage (81%), and elevated platelet count ($450x10^3$/uL; RR 150-400). These results were suggestive of SAT with overt destructive thyrotoxicosis. Erythrocyte sedimentation rate (ESR) was not evaluated. Chest X-ray did not have relevant alterations. Cervical ultrasonography showed a diffusely enlarged thyroid gland, with heterogeneous parenchyma – findings compatible with thyroiditis; no enlarged lymph nodes were detected (Fig. 2).

There was no history of thyroid disease, history of exposure to iodinated contrast or radioactive iodine therapy, recent surgeries or trauma, recent pregnancy or the possibility of being pregnant, nor any pharmacological treatment except for the ibuprofen. There was no known family history of thyroid or autoimmune diseases. All findings were consistent with the diagnosis of SAT, apparently caused by COVID-19. The patient was discharged with prednisolone 40 mg daily as the starting dose, and with referral to Endocrinology for further evaluation. The glucocorticoid tapering scheme instituted was 40 mg daily in the first week, 20 mg daily in the second week, and 10 mg until the consultation. Within a few days of corticosteroid treatment, pain markedly improved, and temperature normalized.

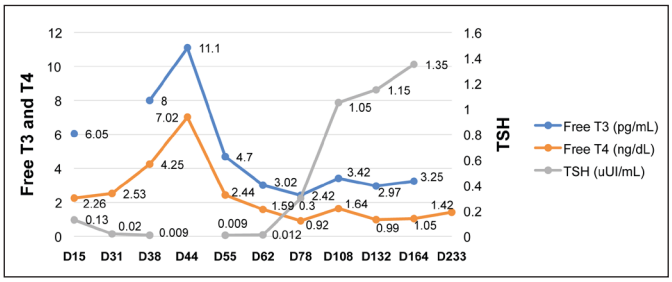

Figure 1. Evolution of thyroid function tests during the follow-up
D – days after the onset of symptoms of infection by SARS-CoV-2.

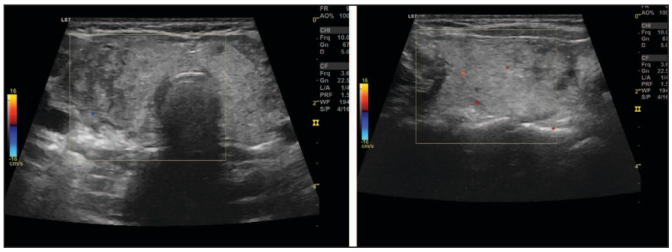

Figure 2. Cervical ultrasonography performed at the emergency department. Diffusely enlarged thyroid gland, with heterogeneous parenchyma and overall decreased vascularization at color Doppler.

She was evaluated at the Endocrinology outpatient clinic for the first time two weeks after ED discharge and 28 days after the diagnosis of COVID-19. Clinically, she reported palpitations, anxiety, and hand tremor. Cervical pain and subfebrile temperature had resolved. Physical examination revealed mild bilateral hand tremor and a visible diffuse goiter with tenderness to palpation (more on the right side, with an apparent palpable nodule). The thyroid was firm, mobile with swallowing, with no bruits, and some cervical lymph nodes, enlarged and tender, were detected on palpation. Thyroid function tests were repeated: TSH 0.016 uUI/mL and FT4 2.53 ng/dL. Because of the symptoms she reported, propranolol 20 mg twice daily was prescribed. She had initiated the 10 mg daily of prednisolone on that day, so it was decided to maintain that dose and reevaluate the patient within a week. However, three days after the first evaluation in the outpatient clinic, the patient contacted the department due to recurrence of the cervical anterior pain with irradiation to the retroauricular and occipital areas, fever (38º-39ºC), and *de novo* odynophagia. The dose of prednisolone was augmented to 20 mg daily and the propranolol was maintained. There was no improvement and three days later (and 34 days after the diagnosis of COVID-19), she went again to the ED. She was discharged with etoricoxib 60 mg daily and paracetamol 1000 mg thrice daily. Four days later, she was reevaluated at the Endocrinology clinic. She maintained all the symptoms, namely, cervical and occipital pain, fever, odynophagia, and sporadic palpitations. Meningeal signs were excluded and laboratory tests showed suppressed TSH levels, high FT4 (4.25 ng/dL), FT3 (8.0 pg/dL) and total triiodothyronine (TT3) (2.45 ng/mL;

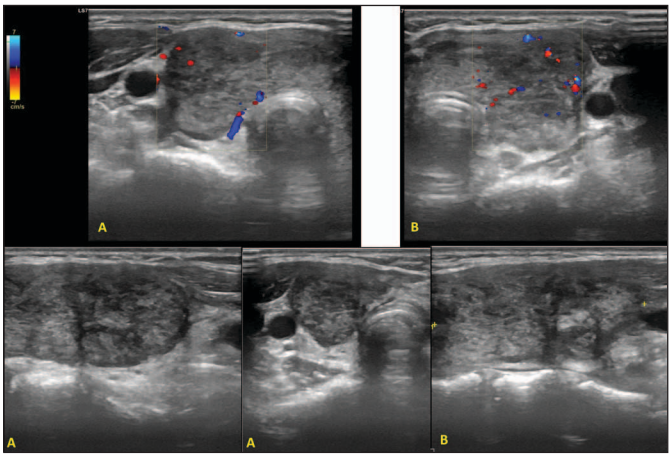

Figure 3. Cervical ultrasonography performed two weeks after the emergency department discharge.
Diffusely enlarged, heterogeneous, and hypoechogenic thyroid gland (volume 22.25cm3) with normal vascularization at color Doppler and multiple pseudonodular areas. A – Right lobe. B – Left lobe.

RR 0.6-1.81); negative anti-thyroglobulin antibodies, anti-peroxidase antibodies, and anti-TSH receptor antibodies levels. Inflammatory markers were elevated [ESR 83 mm/h (RR 1-20); CRP 204.30 mg/L]. Prednisolone and propranolol were augmented to 40 mg daily and 40 mg twice daily, respectively. Two days later, the cervical ultrasonography was repeated (Fig. 3) and showed a diffusely enlarged, heterogeneous, and hypoechogenic thyroid gland (volume 22.25 cm^3) with normal vascularization at color Doppler and multiple pseudonodular areas. The patient reported sustained fever (~39ºC). She was hospitalized the next day, 41 days after the diagnosis of COVID-19 and 36 days after the initial symptoms of SAT appeared. The hospitalization was due to the persistent high fever and intense cervical pain, leading to the suspicion of acute suppurative thyroiditis. Prednisolone 60mg daily and propranolol 40 mg twice daily were prescribed. Cervical and thoracic computed tomography angiography was performed to exclude potential complications such as an abscess. Apart from an enlarged thyroid extending to the superior mediastinum and small jugular-carotid lymph nodes, no other relevant alterations were detected. FT3 (11.1 pg/dL), TT3 (3.76 ng/mL), FT4 (7.02 ng/dL) and thyroglobulin levels (1297 ng/mL; RR 0.73-84) were markedly increased. CRP was 155.2 mg/L, with leukocytosis ($14.9x10^3$/uL) and thrombocytosis ($613x10^3$/uL). Amino-terminal pro-brain natriuretic peptide levels were mildly elevated (359.0 pg/mL; RR <125). Thromboplastin time, activated partial thromboplastin time, phospocalcium metabolism profile, and hepatic and renal function were normal. Blood cultures were negative. An electrocardiogram showed sinus rhythm with a heart rate of 90 beats per minute. During the hospital stay, the patient remained apyretic. She was discharged after four days with prednisolone 60 mg daily and propranolol 40 mg twice daily, and the cervical pain resolved.

The patient was reevaluated one week later. She clinically improved, with no recurrence of pain or fever and with a weight regain of 2 kg, although she still reported palpitations and anxiety. FT3 and FT4 had also decreased, being close to the upper limit of normal. Prednisolone was reduced to 40 mg per day. One week after that, 59 days after the diagnosis of COVID-19 and 54 days after the diagnosis of SAT, FT3 and FT4 normalized and the patient reported only sporadic palpitations and cervical tenderness. Two weeks after, the patient was asymptomatic, with normal FT3 and FT4 levels, and with normal CRP and no leukocytosis or thrombocytosis. Prednisolone was reduced to 30 mg per day, with a slow tapering scheme following that. Glucocorticoid therapy was suspended approximately nine months after the SAT diagnosis.

At the last follow-up, 12 months after the diagnosis of SAT, the patient remained asymptomatic, and thyroid function tests were in the normal range (TSH 1.954 uUI/mL, FT4 1.30 ng/dL).

Discussion

Different mechanisms for thyroid involvement due to SARS-CoV-2 infection can be involved, such as direct virus damage to the organ, systemic inflammation due to cytokines and chemokines, and/or autoimmune reactions.[11,12] Additionally, another important plausible mechanism is that SARS-CoV-2 targets angiotensin-converting enzyme 2 (ACE2), using it as a functional receptor to enter the cells. ACE2 is expressed in various tissues, including thyroid follicular cells, possibly making them susceptible to SARS-CoV-2 entry.[13,14] However, there is still limited available evidence to indicate the pathophysiological pathway of thyroid injury caused by SARS-CoV-2.[6]

We report a case of an atypical SAT, apparently triggered by a SARS-CoV-2 infection. Our case, in addition to others, strongly supports that SARS-CoV-2 should be considered an etiologic agent for the onset of SAT.[5,6] However, although COVID-19 most common manifestations were mild as in the other reported cases,[5,6,15] in our case, the patient presented with an atypical form of SAT, with intense cervical pain, high fever, refractoriness to standard therapy schemes, needing higher doses of corticosteroids, and with a longer duration of the thyrotoxicosis (54 days). We have established the diagnosis of SAT having into consideration the values of thyroid function parameters available and its evolution, the recent upper respiratory viral infection, the characteristics of the cervical pain, the subfebrile/febrile temperature, the progressively worsening of the inflammatory parameters, the initial quick response to glucocorticoid therapy within a few days, and the lack of hypervascularity on color Doppler. Nevertheless, we acknowledge that thyroid scintigraphy would be a relevant exam to perform to help differentiate etiologies of thyrotoxicosis and further establish our diagnosis of SAT. This exam was not considered initially as its execution in our institution would not be promptly.

We acknowledge that the initial glucocorticoid tapering approach used was not conventional, and that this strategy might raise concerns. Generally, the clinical course of SAT is mild and self-limited and treatment with nonsteroidal anti-inflammatory agents (NSAIDs) and β-adrenergic-blocking drugs is recommended.[16] Antithyroid drugs do not have a role in the treatment of SAT. Use of corticosteroids is limited to patients who do not respond to NSAIDs over several days of use or present with moderate to severe pain and/or symptoms of thyrotoxicosis, as was the case for our patient.[16] The standard recommendations by the American Thyroid Association (ATA) for corticosteroid therapy in SAT are prednisone 40 mg per day for 1-2 weeks followed by a gradual tapering scheme over 2-4 weeks or longer, depending on the clinical response.[16]

Nevertheless, we believe the approach instituted does not justify the more exuberant and atypical clinical course of our SAT case. Firstly, our patient had self-medicated with a high dose of NSAID for seven days, the first-line therapy recommended by the ATA for SAT, but the symptoms persisted and gradually worsened with severe cervical discomfort and fever. Secondly, prednisolone 40 mg per day was initiated but higher doses were needed (maxi-

mum daily dosage: 60 mg). Most of the previous reports of SAT associated with COVID-19 used initial lower doses of prednisolone (most commonly 25 mg daily, n=12 out of 27 reported cases) without needing higher doses. The remaining patients n=2 were treated with a lower dose of prednisolone (16 and 20 mg), n=2 were treated with aspirin, and n=3 were treated exclusively with NSAID. Only five patients were initially treated with higher doses of prednisolone (n=2 prednisolone 40 mg/day, n=1 prednisolone 30 mg/day, n=1 dexamethasone 4 mg every 8 hours for 5 days, n=1 methylprednisolone 40 mg/day for 3 days).[6,15] In addition to this, based on the available published data, it appears that, once recognized, SAT associated with COVID-19 does not requires a different treatment approach when compared with non-COVID-19 cases.[17] So, lastly, the basis for the recommend titration scheme by ATA was not established by prospective studies. In a prospective study performed by Sharma *et al*.[18] it was shown that 20 mg of prednisolone per day tapered over four weeks is an adequate treatment of SAT, with symptoms resolving in two weeks in 94% of the patients, with a low recurrence rate (7.3%). Their cohort after two weeks was initiated with 10 mg of prednisolone, like our patient. Additionally, previous research had already demonstrated that prednisolone 15 mg per day with a tapering scheme of 5 mg every two weeks is a safe and effective mean to quickly reduce the pain in SAT, being that specific study referred in the ATA.[16,19] Recently, a systematic review and meta-analysis was published with the objective to identify the lowest effective initial dose of prednisolone for the treatment of subacute granulomatous thyroiditis.[20] They concluded that 15 to 20 mg per day of prednisolone was the most effective dose with the lowest recurrence rate in the treatment of SAT. Additionally, iIt is well-established that glucocorticoids are beneficial for relieving SAT symptoms more quickly and for reducing the recurrence rate, and, in more serious manifestations of COVID-19, this type of treatment improves the outcomes, namely the mortality rate.[21] Taking this into account, we hypothesize that small doses of glucocorticoids might be a more appropriate treatment option than NSAIDs for SAT caused by SARS-CoV-2. In conclusion, it seems that our patient was initiated with a higher dose than she theoretically needed according with the current literature. Nevertheless, we recognized, as abovementioned, that the reduction from 40 to 10 mg in two weeks was not ideal, and we cannot exclude it might partially have contributed to a progression of the symptoms, as it is known that symptoms can recur as the dose of corticosteroid is reduced.[22] Still, in this case, exuberant, long-lasting and *de novo* clinical symptoms emerged; it was not exclusively a recurrence of previous reported symptoms.

On the contrary, we believe that the second tapering approach was excessively long. This was due to several factors. Firstly, in January 2021, the available evidence on this subject was scarce, with few published case reports and no consolidated knowledge or recommendations in terms of the treatment approach of this entity. Secondly, the SAT in our patient had an atypical presentation, with a longer duration of thyrotoxicosis, more exuberant symptoms, refractiveness to the standard first-line treatment and the need for higher doses of prednisolone. Thirdly, the initial tapering approach possibly was too quick for this specific case, as previously discussed, and we did not know at the time the influence of that initial titration in the natural evolution of the disease, so we decided to not repeat a short treatment period, which might have been an overzealous approach. Fourthly, the patient was under a high dose of prednisolone for Lastly, after the need for hospital admission, the patient was fearful the symptoms would recur with the reduction of the dosage, the inflammatory parameters were elevated for several weeks after discharge, and she experienced residual cervical discomfort with the first new titrating of dose, contributing to our decision for a more conservative tapering scheme and a longer clinical surveillance in our department. Additionally, we would like to add that in the last six months the patient was with a low dosage of corticosteroid (hydrocortisone 5 mg daily for two months and in alternate days for four months) and the patient asked for the reschedule of one of the consultations, delaying the suspension of the therapy by three months.

The atypical form of SAT that occurred in our case could be potentially justified by various factors, namely, the specific SARS-CoV-2 variant she presented and her vaccinal status. As our patient was diagnosed with COVID-19 in December 2020, the information available then regarding SARS-CoV-2 variants was scarce, and the variant she contracted is unknown. Additionally, at that time, the patient was not eligible to receive the vaccine for COVID-19. According to The National Health Institute Doutor Ricardo Jorge, in December 2020, the most common variant in Portugal was variant 20A.EU1 (S:A222V) - responsible for 67% of the cases - followed by 20A.EU2 variant (8.7%) and various other less frequent variants.[23] Nonetheless, there are no published studies specifically comparing SAT's incidence and severity between variants of SARS-CoV-2. We hypothesize that there might exist differences in terms of susceptibility to SAT and its presentation, as there is evidence in model animals showing that different SARS-CoV-2 variants associate with varying clinical manifestations of COVID-19, due to differences in pathogenicity, immune activation, and organ tropism.[24] In humans, however, these findings and comparisons were performed in more recent variants such as Omicron and Delta.[25-27] Regarding vaccinal status, there is no evidence comparing the risk or severity of SAT SARS-CoV-2-related between immunized and non-immunized patients. However, there is a new entity – SAT following the vaccine for COVID-19. It is known that SAT after immunization is typically less symptomatic than SAT for other causes and is associated with good long-term outcomes. Previous infection with SARS-CoV-2 as not been associated with an increased nor a decrease in the risk to develop this disease after vaccination.[17] Therefore, we can only speculate that if the patient was immunized, she might have had a less exuberant form of SAT.

In an article reviewing the early and late endocrine complications of COVID-19, thyroid gland dysfunction was evaluated and eight studies reporting SAT associated with COVID-19 were included (n=23).[5] Notably, like our patient, all the patients in this study had non-severe COVID-19 infection symptoms, with only mild fever and upper respiratory tract symptoms and none needed to be admitted to intensive care units. The symptoms of SAT were typical and included fever, anterior cervical pain, fatigue, tremors, sweating, and palpitations, while the time between COVID-19 diagnosis and typical SAT symptoms ranged between 5 and 42 days. Many of these patients presented with typical SAT ultrasonographic features.[5,28] Most of the patients were treated with corticosteroids (prednisolone 25 mg/day), and the symptoms improved within a few days; thyroid function normalized after 1 to 2 months. There was no report of recurrence of symptoms or a more severe form of SAT than expected.

As time goes on, mounting evidence emerges describing new clinical manifestations are being attributable to COVID-19 disease. To this date, and to the best of our knowledge, SAT SARS-CoV-2-related is apparently a rare complication of COVID-19 disease, as in a recent review article from 2022, only 81 cases were reported worldwide.[17] Consequently, there is still contradicting evidence re-

lated to this new entity. The abovementioned review article states that differences among other forms of SAT still need to be established since the available statistical evidence is scarce.[17] However, it seems that, in most of the cases, the clinical manifestations are indeed similar to SAT associated with other viral infections, and it does not require a distinct treatment approach.[17]

We believe that our case, by the severity, long duration of the symptoms, and need of high doses of glucocorticoids, should raise the hypothesis that atypical manifestations of SAT might arise in patients with mild or asymptomatic forms of COVID-19, and we should be more alert to alterations in thyroid function even in milder presentations of SARS-CoV-2 infection. In fact, this could be a specific marker of this virus. This hypothesis was previously proposed by Brancatella *et al*,[29] but other authors state that not all the available data supports this statement.[17] This same article refers that less severe manifestations of SAT are seen in patients with mild infection, as opposed to our case.

In conclusion, although it is a rare entity, our case highlights the importance of considering SARS-CoV-2 infection as a potential trigger for SAT. Clinicians should be alerted to this diagnosis; and should be aware that more severe, refractory to the standard treatment, and long-lasting manifestations of SAT may occur, even in the presence of mild forms of COVID-19.

Contributorship Statement / Declaração de Contribuição:

S Campos Lopes: conceptualization, data collection, writing original draft, and final approval.
J Marques Sá, V Fernandes, C Machado: data collection, review, and final approval.
AM Monteiro: conceptualization, supervision, review, and final approval.

Responsabilidades Éticas

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References / Referências

1. Wang Z, Deng H, Ou C, Liang J, Wang Y, Jiang M, Li S. Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: A systematic review and meta-analysis without cases duplication. Medicine. 2020;99:e23327. doi: 10.1097/MD.0000000000023327.
2. Lusczek ER, Ingraham NE, Karam BS, Proper J, Siegel L, Helgeson ES, et al. Characterizing COVID-19 clinical phenotypes and associated comorbidities and complication profiles. PLoS One. 2021;16:e0248956. doi: 10.1371/journal.pone.0248956.
3. Sharifian-Dorche M, Huot P, Osherov M, Wen D, Saveriano A, Giacomini PS, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. J Neurol Sci. 2020;417:117085. doi: 10.1016/j.jns.2020.117085.
4. Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, et al. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. World J Gastroenterol. 2020;26:4579-88. doi: 10.3748/wjg.v26.i31.4579.
5. Kazakou P, Paschou SA, Psaltopoulou T, Gavriatopoulou M, Korompoki E, Stefanaki K, et al. Early and late endocrine complications of COVID-19. Endocr Connect. 2021;10:R229-39.
6. Chen W, Tian Y, Li Z, Zhu J, Wei T, Lei J. Potential Interaction Between SARS-CoV-2 and Thyroid: A Review. Endocrinology. 2021;162:bqab004. doi: 10.1210/endocr/bqab004.
7. Nishihara E, Ohye H, Amino N, Takata K, Arishima T, Kudo T, et al. Clinical characteristics of 852 patients with subacute thyroiditis before treatment. Intern Med. 2008;47:725-9.
8. Benbassat CA, Olchovsky D, Tsvetov G, Shimon I. Subacute thyroiditis: clinical characteristics and treatment outcome in fifty-six consecutive patients diagnosed between 1999 and 2005. J Endocrinol Invest. 2007;30:631-5.
9. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J. 2009;6:5.
10. Latrofa F, Ricci D, Montanelli L, Altea MA, Pucci A, Pinchera A, Vitti P. Thyroglobulin autoantibodies of patients with subacute thyroiditis are restricted to a major B cell epitope. J Endocrinol Invest. 2012;35:712-4.
11. Parolin M, Parisotto M, Zanchetta F, Sartorato P, De Menis E. Coronaviruses and endocrine system: a systematic review on evidence and shadows. Endocr Metab Immune Disord Drug Targets. 2021;21:1242-51. doi: 10.2174/1871530320666200905123332.
12. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord. 2020;21:495-507. Erratum in: Rev Endocr Metab Disord. 2021;22:145. doi: 10.1007/s11154-020-09569-2.
13. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis. 2021;40:905-19. doi: 10.1007/s10096-020-04138-6.
14. Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST,et al. Detection of SARS-CoV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. J Endocrinol Invest. 2021;44:1085-90. doi: 10.1007/s40618-020-01436-w.
15. Trimboli P, Cappelli C, Croce L, Scappaticcio L, Chiovato L, Rotondi M. COVID-19-associated subacute thyroiditis: evidence-based data from a systematic review. Front Endocrinol. 2021;12:707726. doi: 10.3389/fendo.2021.707726.
16. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL,et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26:1343-421.
17. Popescu M, Ghemigian A, Vasile CM, Costache A, Carsote M, Ghenea AE. The new entity of subacute thyroiditis amid the COVID-19 pandemic: from infection to vaccine. Diagnostics. 2022;12:960. doi: 10.3390/diagnostics12040960.
18. Koirala KP, Sharma V. Treatment of acute painful thyroiditis with low dose prednisolone: a study on patients from Western Nepal. J Clin Diagn Res. 2015;9:MC01-3.
19. Kubota S, Nishihara E, Kudo T, Ito M, Amino N, Miyauchi A. Initial treatment with 15 mg of prednisolone daily is sufficient for most patients with subacute thyroiditis in Japan. Thyroid. 2013;23:269-72.
20. Soltani A, Nourani F, Roudsari SB, Jouybari L, Fathi M, Haghighat S,et al. Identifying the lowest effective initial dose of prednisolone for the treatment of subacute granulomatous thyroiditis: a systematic review and meta-analysis. Curr Rev Clin Exp Pharmacol. 2022;17:135-43. doi: 10.2174/2772432816666211012092112.

21. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693-704.
22. Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ.Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab.2003;88: 2100–5. doi: 10.1210/jc.2002-021799.
23. Instituto Nacional de Saúde Dr. Ricardo Jorge. Diversidade genética do novo coronavírus SARS-CoV-2 (COVID-19) em Portugal [accessed May 5th 2022] Available at: https://insaflu.insa.pt/covid19/relatorios/INSA_SARS_CoV_2_DIVERSIDADE_GENETICA_relatorio_situacao_2020-12-28.pdf
24. Stolp B, Stern M, Ambiel I, Hofmann K, Morath K, Gallucci L, et al. SARS-CoV-2 variants of concern display enhanced intrinsic pathogenic properties and expanded organ tropism in mouse models. Cell Rep. 2022;38:110387. doi: 10.1016/j.celrep.2022.110387.
25. Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, et al. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in tshwane, south africa. Int J Infect Dis. 2022;116:38-42. doi: 10.1016/j.ijid.2021.12.357.
26. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves. JAMA. 2022;327:583-4. doi: 10.1001/jama.2021.24868.
27. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. Lancet. 2022;399:1618-24. doi: 10.1016/S0140-6736(22)00327-0.
28. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol. 2020;8:739-41. doi: 10.1016/S2213-8587(20)30266-7.
29. Brancatella A, Viola N, Rutigliano G, Sgrò D, Santini F, Latrofa F. subacute thyroiditis during the SARS-CoV-2 pandemic. J Endocr Soc. 2021;5:bvab130. doi: 10.1210/jendso/bvab130.

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Caso Clínico

Surgical Cytoreduction Against Malignant Pheochromocytoma: Case Report

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Radiopharmaceuticals/therapeutic use.

A B S T R A C T

Pheochromocytoma is a rare pathology, even more so its malignant presentation. It is an aggressive entity but with an acceptable survival, liable to palliative treatment with good results. Currently available therapeutic options are surgical debulking, radiopharmaceutical therapy (IMIBG Y and Lu-DOTATATE), chemotherapy and targeted therapy. The timing at which metastatic patients benefit most from systemic therapy has not yet been established. However, at some point they will require resective surgical treatment.
Expectant management is accepted whenever is possible. When the symptomatology is flowery and difficult to manage medically, the therapeutic range is imposed being the treatment option a combination between surgical reduction and 131I-MIBG.

Palavras-chave:
Compostos Radiofarmacêuticos/uso terapêutico;
Feocromocitoma/tratamento;
Procedimentos Cirúrgicos de Citorredução.

Citorredução Cirúrgica Contra Feocromocitoma Maligno: Relato de Caso

R E S U M O

O feocromocitoma é uma patologia rara, ainda mais sua manifestação maligna. É uma entidade agressiva mas com uma sobrevida aceitável, sujeita a tratamento paliativo com bons resultados.
As opções terapêuticas atualmente disponíveis são a citorredução cirúrgica, terapia radiofarmacêutica (I-MIBG Y e Lu-DOTATATE), quimioterapia e terapia direcionada. O momento em que os pacientes metastáticos mais se beneficiam da terapia sistêmica ainda não foi estabelecido. No entanto, é claro que em algum momento eles necessitarão de tratamento cirúrgico ressectivo.
Tratamentos expectantes são aceitos sempre que possível. Quando a sintomatologia é rebuscada e de difícil manejo médico, o leque terapêutico é definido de modo a escolher a combinação de redução cirúrgica e 131IMIBG.

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Introduction

Catecholamine-producing tumors originating from chromaffin cells of adrenal topography are known under the name of pheochromocytomas, a rare entity that can manifest itself in the context of other familial hereditary syndromes (25%).[1]

Those that occur in extra-adrenal tissue are called paragangliomas, being important the distinction between the two. The highest incidence is between the fourth and fifth decades of life, without gender predominance. These are usually asymptomatic tumors and their finding is incidental (incidentaloma).[2]

The classic symptomatic presentation is the well-known triad consisting of headache (80%), palpitations (64%) and diaphoresis (57%),[3] a, which depends on the production of catecholamines. Diagnostic confirmation is performed by measuring catecholamines, plasmatic and in 24-hour urine metanephrines.

Tumor localization requires imaging study. Computed tomography shows the lesion as unique, heterogeneous, oval, with a coefficient of attenuation without contrast greater than 10 Hounsfield units (HU).[4]

Magnetic resonance imaging is mainly used in children or pregnant women, being characteristic the unique hyperintense image in T2.

Those classified as malignant, are defined as such with distant metastases at the time of diagnosis or years later in evolution. It is estimated that 10%-20% of pheochromocytomas are malignant.[5] These patients should be studied using functional imaging methods such as scintigraphy and positron emission tomography.

The scintigraphy is performed with isotopes 123IMIBG or 131I-MIBG, the former being preferable due to its shorter half-life and greater sensitivity (83%). The use of both isotopes increases sensitivity to 100%.6

In some cases, inconclusive for metastasis, maybe necessary to perform a PET scan with 18F-FDG or 18F-FDA. Therefore, several studies propose higher performance of PET with 18F-FDA compared to 123I-MIBG for the assessment of metastatic disease.[7]

Treatment is essentially surgical for either pheochromocytoma or metastatic lesions and involves complete resection of the lesion.

Case Report

Male, 57 years old with a history of pheocromocitoma operated 8 years ago. During control assessment, patient begins with high blood pressure. Catecholamines, metanephrines and vanilmandelic acid were requested. It stands out from these: elevated metanephrines and ac vanilmandelic of 18.2 mg /24 hours (normal less than 8 mg/24 hours).

Assessment is completed with magnetic resonance imaging (MRI) that shows three solid lesions of 19, 5 and 7 mm in the hepatic segment 7 hypointense in T1, intermediate in T2; and multiple solid peritoneal nodules (hypointensum in T1, intermediate in T2, of variable size between subcentimeters to 30 mm nodule).

Endoscopic studies (fibrogastroduodenoscopy and colonoscopy) did not show any alterations.

The evaluation was complemented with PET 18F-FDG showing peritoneal nodules without catchment. PET Ga-DOTATATE revealed multiple lesions compatible with peritoneal implants with great avidity for radiotrace and therefore express somatostatin receptors.

Genetic tests have not been performed because the patient does not have access to them.

In multidisciplinary discussion, it is proposed surgical treatment previous alpha and beta blockage.

The presence of multiple peritoneal implants stands out from the surgical procedure, with a predominance of the visceral peritoneum, being enteric and mesial juxta in greater numbers (Figs. 1 and 2). It was performed a complete resection without macroscopic remnants (Fig. 3) with a favorable postoperative evolution.

In quarterly control, slight rise of metanephrines without accompanying symptoms.

Assessment was completed with PET-CT that evidenced persistence of peritoneal implant with expression of somatostatin receptors, in close relationship with the hepatic segment 6 and of at least two mesenteric nodules up to 8 mm one of them hypercaptive.

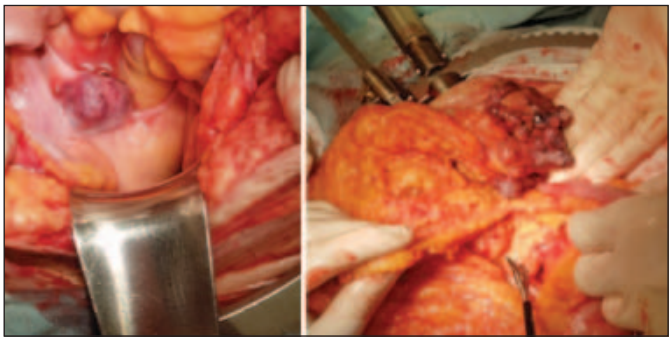

Figure 1. Multiple peritoneal implants.

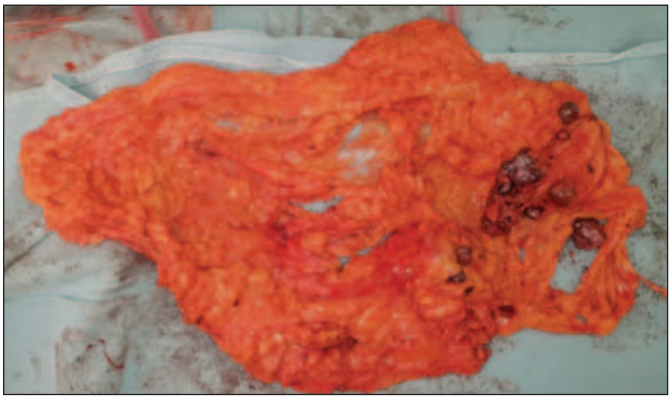

Figure 2. **Piece of resection-omentectomy**.

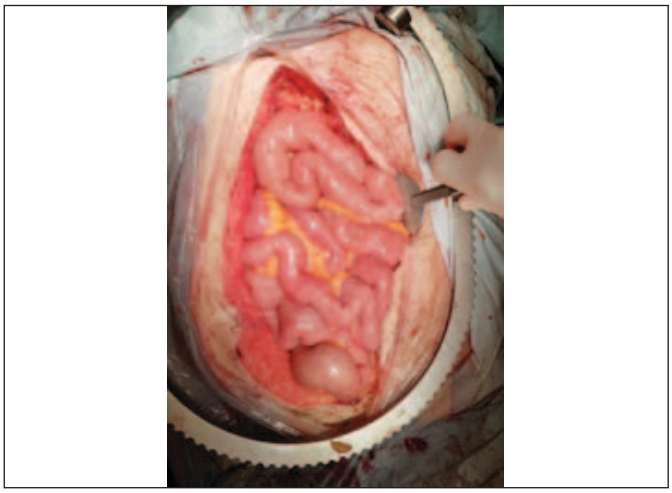

Figure 3. **Result after debulking (omentectomy and resection of all macroscopic lesion were performed).**

Consequently, he was treated with 131I-MIBG and had been monitored progress with SPECT-CT (131I MIBG) which shows a partial response to metabolic radiotherapy (Fig. 4).

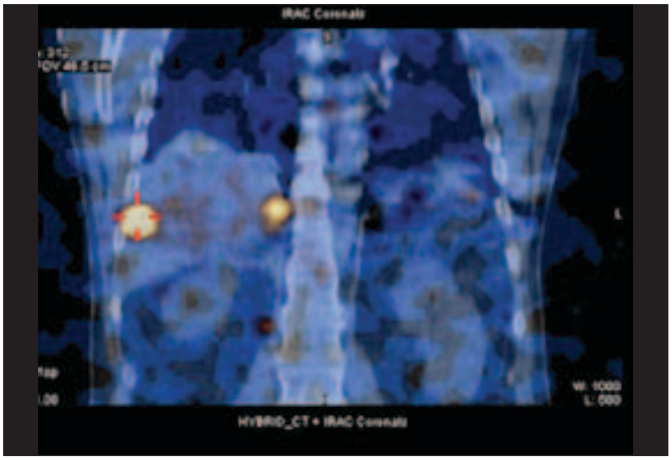

Figure 4. **MIBG con SPECT-CT (131I MIBG).**

Discussion

Approximately 10% of pheochromocytomas are malignant, with the presence of metastases at the time of diagnosis or up to 20 years later, which certifies the emergence of malignancy. The natural course of metastatic disease is very heterogeneous, with an overall survival rate at 5 years ranging between 40% and 85%, with its evolution difficult to predict.

Management of metastatic pheochromocytoma remains a challenge. So much so, that recent

Studies[8] propose that the elaboration of gene expression and methylation profiles can allow these patients to be characterized in groups with the aim of guiding therapy more effectively.

Recent work regarding the molecular characteristics of pheochromocytomas and paragangliomas reports that more than 30%-40% of them are associated with inherited genetic abnormalities involving more than 20 genes, including *SDHX*, *RET*, *VHL*, *NF1*, *TMEM127*, *MAX* and others. Such genetic alterations are primarily involved in the pathogenesis of pseudohypoxia, Wnt signaling, and kinase.[9]

Currently available therapeutic options are surgical debulking, radiopharmaceutical therapy (IMIBG, Y and Lu-DOTATATE), chemotherapy and targeted therapy. The timing at which metastatic patients benefit most from systemic therapy has not yet been established. However, at some point they will require resective surgical treatment.[10]

131IMIBG is considered today as the most effective treatment along with surgery, so that it has been recommended as a first-line treatment in patients with slow-growing metastatic lesions as well as against relapses or tumor persistence. Chemotherapy with cyclophosphamide, vincristine and dacarbazine, achieves a radiological response in half of the cases, with good hormonal response and an average survival rate of almost two years. Treatment with 177Lu-octreotide has been effective in some patients and is useful in tumors that do not capture 131I-MIBG or in combination with it as they may have a synergistic effect.

Targeted therapy with tyrosine kinase inhibitors manifests itself as a vision for the future in full development. Preliminary results from a phase II11 clinical trial with cabozantinib showed partial response/disease stabilization in 93% of the 14 patients included. Multiple early-stage clinical trials evaluate the efficacy of different therapeutic options including immunotherapy, radiopharmaceuticals and peptide receptors, seeking greater survival in this group of patients.[12]

Conclusion

Pheochromocytoma is a rare pathology, even more so its malignant presentation. It is an aggressive entity but with an acceptable survival, subject to palliative treatment with good results.

Expectant management whenever possible is a priority.

When the symptomatology is flowery and difficult to manage medically, the therapeutic range is imposed being the treatment option a combination between surgical reduction and 131I-MIBG.

Contributorship Statement / Declaração de Contribuição:

CG and UP: Conceptualization, data collection, writing original draft, and final approval.
CB: Conceptualization, methodology, supervision, review and final approval.
JB: Conceptualization, data collection, review and final approval.

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References / Referências

1. Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, et al. Germ-line mutations in nonsyndromic phechromocytoma. N Engl J Med. 2002;346:1459-66. doi: 10.1056/NEJMoa020152.
2. Bravo EL, Tagle R. Pheochromocytomas: State of the art and future prospects. Endocr Rev. 2003;24:539-53. doi: 10.1210/er.2002-0013.
3. Motta-Ramirez GA, Remer EM, Herts BR Gill IS, Hamrahian AH. Comparison of CT findings in symptomatic and incidentally discovered

pheochromocytomas. AJR Am J Roentgenol. 2005;185:684-8. doi: 10.2214/ajr.185.3.01850684.

4. Dunnick NR, Korobkin M. Imaging of adrenal incidentalomas: current status. AJR Am J Roentgenol. 2002;179:559-68. doi: 10.2214/ajr.179.3.1790559.
5. Arias Martínez N, Barbado Hernández FJ, Couto Caro R, Gil Guerrero L, Coronado Poggio M, Navarro T, et al. Malignant pheochromocytoma treated with MIBG I131. An Med Intern. 2003; 8:575-8.
6. van der Harst E, de Herder WW, Bruining HA, Bonjer HJ, de Krijger RR, Lamberts SW, et al. [(123)I]metaiodobenzylguanidine and [(111)In] octreotide uptake in begnign and malignant pheochromocytomas. J Clin Endocrinol Metab. 2001;86:685-93. doi: 10.1210/jcem.86.2.7238.
7. Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, GimenezRoqueplo AP, Grossman AB, et al. Pheochromocytoma: recommendations for clinical practice from the First International Symposium. Nat Clin Prac End Metab. 2007;3:92-102. doi: 10.1038/ncpendmet0396.
8. Corssmit EP, Snel M, Kapiteijn E. Malignant pheochromocytoma and paraganglioma: management options. Curr Opin Oncol. 2020;32:20-6. doi: 10.1097/CCO.0000000000000589.
9. Yamazaki Y, Gao X, Pecori A, Nakamura Y, Tezuka Y, Omata K, et al. Recent Advances in Histopathological and Molecular Diagnosis in Pheochromocytoma and Paraganglioma: Challenges for Predicting Metastasis in Individual Patients. Front Endocrinol. 2020;11:587769. doi: 10.3389/fendo.2020.587769.
10. Hescot S, Leboulleux S, Amar L, Vezzosi D, Borget I, Bournaud-Salinas C, et al. One-year progression-free survival of therapy-naive patients with malignant pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2013;98:4006-12. doi: 10.1210/jc.2013-1907.
11. Jimenez C. A phase 2 study to evaluate the effects of cabozantinib in patients with unresectable metastatic pheo-chromocytomas and paragangliomas. Endocr Pract. 2018; 24:25.
12. Hamidi O. Metastatic pheochromocytoma and paraganglioma: recent advances in prognosis and management. Curr Opin Endocrinol Diabetes Obes. 2019;26:146-54. doi: 10.1097/MED.0000000000000476.

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Caso Clínico

Fraturas Osteoporóticas e Síndrome 48XXYY: Caso Clínico

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R E S U M O

A síndrome 48,XXYY caracteriza-se pela presença de cromossomas X e Y extras e clinicamente por estatura alta, infertilidade, hipogonadismo, perturbações do neurodesenvolvimento e comportamentais e risco aumentado de malformações congénitas.
Um homem de 46 anos foi referenciado por fractura osteoporótica da anca esquerda. Tinha história de epilepsia, esofagite de refluxo, dislipidemia, perturbação do desenvolvimento intelectual e uma fratura osteoporótica da anca direita. Nunca tinha efectuado tratamento anti-osteoporótico. O exame físico revelou dismorfias faciais inespecíficas, obesidade central, diminuição da barba, ginecomastia e atrofia testicular. A avaliação analítica revelou insuficiência em vitamina D e hipogonadismo hipergonadotrófico; o resultado do estudo do cariótipo do sangue periférico foi 48,XXYY. Efectuou tratamento com ácido zoledrónico, testosterona intramuscular e suplementação oral de cálcio e vitamina D.
A síndrome 48,XXYY, antes considerada uma variante da síndrome de Klinefelter, é hoje descrita como uma entidade clínica e genética distinta. O hipogonadismo predispõe os doentes à osteoporose e às fracturas de fragilidade.

Keywords:
Chromosomes, Human, X;
Chromosomes, Human, Y;
Klinefelter Syndrome/genetics;
Osteoporotic Fractures.

Osteoporotic Fractures and 48XXYY Syndrome: Clinical Case

A B S T R A C T

48,XXYY syndrome is characterized by the presence of extra X and Y chromosomes and clinically by tall stature, dysfunctional testicles associated with infertility and hypogonadism, developmental delay, behaviour disorders and increased risk of congenital malformations.
A 46-year-old man was referred due to an osteoporotic fracture of the left hip. He had epilepsy, reflux esophagitis, dyslipidemia, intellectual disability, and a previous osteoporotic fracture of the right hip. He had never been treated with anti-osteoporotic drugs. Physical examination revealed nonspecific dysmorphic features, central obesity, reduced facial hair, gynecomastia, and testicular atrophy. Biochemical evaluation showed vitamin D insufficiency and hypergonadotropic hypogonadism; karyotype study revealed 48,XXYY. He started treatment with zoledronic acid, intramuscular testosterone, oral calcium and vitamin D supplementation.
48,XXYY syndrome, previously considered a variant of Klinefelter syndrome, is now described as a distinct clinical and genetic entity. Hypogonadism predisposes these patients to osteoporosis and fragility fractures.

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Introdução

A síndrome 48,XXYY é uma anomalia cromossómica que resulta da existência de dois cromossomas sexuais extras, um X e um Y, em indivíduos fenotipicamente do sexo masculino. A sua ocorrência é extremamente rara, com uma incidência de cerca de 1 caso em cada 18 000 a 50 000 nascimentos.[1] As crianças com a síndrome 48,XXYY apresentam características semelhantes às da síndrome de Klinefelter, mas diferem da mesma por apresentarem geralmente um quadro clínico mais complexo e maior prevalência de perturbações do neurodesenvolvimento, problemas comportamentais e patologias do foro neuropsiquiátrico.[2] Clinicamente estes doentes podem apresentar alta estatura, disfunção testicular, infertilidade, hipogonadismo, perturbações do neurodesenvolvimento, problemas comportamentais, perturbações neuropsiquiátricas e risco de malformações congénitas, o que torna o diagnóstico precoce muito importante, pois permitem-nos adoptar medidas para prevenir, diagnosticar e tratar as comorbilidades associadas a esta síndrome de forma mais célere e assim, prevenir complicações como a osteoporose. Porém, apesar do atraso global do desenvolvimento ou de outras perturbações do neurodesenvolvimento que estes doentes apresentam, muitos destes casos ainda chegam à vida adulta sem serem diagnosticados, pelo que é necessário sensibilizar os profissionais de saúde para a importância da investigação etiológica e/ou da referenciação precoce para as consultas apropriadas das crianças com este tipo de manifestações.

Caso Clínico

Um homem de 46 anos de idade, foi referenciado à Consulta Multidisciplinar de Osteoporose Fracturária devido a uma fractura do colo do fémur esquerdo.

O evento fracturário havia ocorrido dois meses antes, em consequência de uma queda da própria altura. Recorreu ao Serviço de Urgência, onde foi diagnosticado com fractura transcervical do fémur esquerdo e foi submetido a fixação *in situ* com 3 parafusos canulados.

O doente residia num centro de apoio a pessoas com deficiência, onde participava em actividades lúdicas e recreativas, incluindo trabalhos manuais, exercícios cognitivos, actividade física e tinha acompanhamento psicossocial e dos serviços de saúde e reabilitação.

O seu histórico médico incluía epilepsia, perturbação do desenvolvimento intelectual, esofagite de refluxo, dislipidemia, enfisema pulmonar, e uma fractura osteoporótica do colo do fémur direito aos 43 anos de idade. Estava medicado com carbamazepina 200 mg/dia, ácido acetilsalicílico 100 mg/dia, pantoprazol 40 mg/dia e sinvastatina 20 mg/dia. Negava hábitos tabágicos ou alcoólicos. Apresentava uma ingestão diária de cerca de 500 mg de cálcio (em média 2 copos de leite) e não tinha antecedentes familiares de fracturas osteoporóticas.

Ao exame objectivo apresentava-se orientado, com discurso coerente embora com algum défice de atenção e hiperactividade. Ao exame físico além da marcha apoiada em duas canadianas, destacava-se: dismorfias faciais inespecíficas (nariz comprido, lábios finos, ligeiro prognatismo), obesidade central, redução da barba, ligeira atrofia muscular dos membros inferiores e atrofia testicular bilateral com volumes testiculares direito e esquerdo de 5 e 6 mL respectivamente. Peso 91 kg, estatura 1,65 m, IMC 33,7 kg/m^2.

A avaliação analítica encontra-se descrita na Tabela 1.

Tabela 1. Avaliação analítica.

Avaliação Analítica	Resultados	Valores de Referência
Cálcio	9,5	9,6 – 10,2 mg/dL
Fósforo	3,4	2,5 – 4,5 mg/dL
25-OH-Vitamina D	18,1	>30 ng/mL
N-MID osteocalcina	24,1	14 – 42 ng/mL
P1NP	70,8	< 50 ng/mL
CTX	0,60	0,13 – 0,57 ng/mL
T4 livre	0,93	0,85 – 1,70 ng/dL
TSH	2,44	0,30 – 4,20 uU/mL
PTH	45,8	14 – 72 pg/mL
FSH	18,7	1,5 – 12,9 U/L
LH	14,8	1,7 – 8,6 U/L
Testosterona Total	46,6	240 – 830 ng/dL
Testosterona Livre	2,09	15 – 50 pg/mL

A densitometria óssea revelou osteoporose grave, com T-*score* e Z-*score* na coluna lombar de -3,0 e -3,2, respectivamente (Fig. 1).

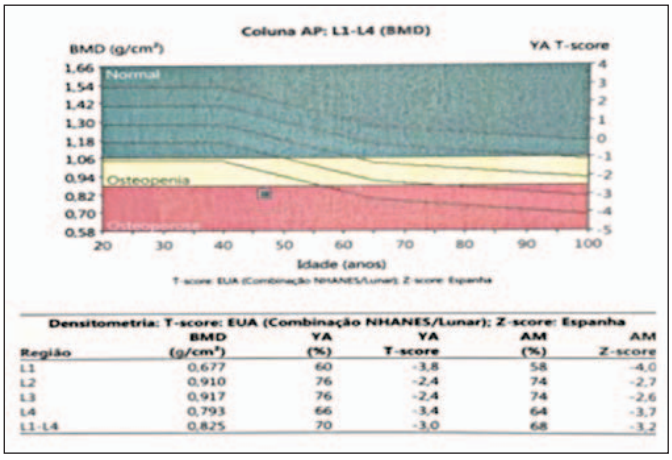

Figura 1. Densidade mineral óssea medida na coluna lombar (L1-L4) por densitometria bifotónica.

O estudo do cariótipo em sangue periférico identificou uma aneuploidia dos cromossomas sexuais em todas as células analisadas, especificamente um cromossoma X e um cromossoma Y supranumerários, correspondendo à síndrome 48,XXYY.

Iniciou tratamento com ácido zoledrónico por via intravenosa 5 mg a cada 12 meses, enantato de testosterona 250 mg por via intramuscular a cada 3 semanas e suplementação por via oral com carbonato de cálcio 1000 mg/dia e colecalciferol 800 UI/dia. Verificou-se boa adesão ao tratamento e não se registaram efeitos adversos.

Associado ao tratamento farmacológico, foram incentivadas mudanças no estilo de vida assim como medidas para evitar a ocorrência de quedas.

Discussão

O caso clínico apresentado refere-se a um homem de 46 anos de idade, com fraturas patológicas bilaterais do colo do fémur ocorridas num período de 3 anos, sem nunca ter sido medicado para a osteoporose. Estas fraturas terão resultado da fragilidade e da baixa qualidade ósseas causadas pela osteoporose.

A osteoporose é uma doença metabólica do osso caracterizada por redução da massa óssea e alterações na microarquitetura óssea

que torna os doentes mais suscetíveis à ocorrência de fraturas.[3] É mais prevalente em idosos, nomeadamente nas mulheres após a menopausa. Estima-se que uma em cada três mulheres e um em cada cinco homens sofrerá uma fratura osteoporótica durante a vida, sendo a fratura da anca a que apresenta um pior prognóstico.[4,5]

Na osteoporose secundária estão subjacentes patologias, tóxicos ou fármacos que originam perda de massa óssea.[6] A sua presença suspeita-se perante a ocorrência de fraturas de fragilidade em homens mais jovens ou mulheres na pré-menopausa, fraturas de novo apesar do cumprimento da terapêutica anti-osteoporótica e quando o Z-*score* é muito baixo.[7] Em alguns estudos, 20% a 30% das mulheres na pós-menopausa e mais de 50% dos homens com osteoporose têm uma causa secundária.[8] Uma das principais causas de perda de massa óssea nos homens é a redução da testosterona livre. Outras causas secundárias de perda de massa óssea são: iatrogenia, doenças endócrinas como hiperparatiroidismo e hipertiroidismo, síndromes de malabsorção, doenças inflamatórias crónicas, neoplasias e transplantação.[9]

O facto de o doente apresentar fraturas osteoporóticas consideradas graves e que normalmente ocorrem em idosos associado às características fenotípicas de hipogonadismo, sugeria a existência de uma causa secundária de osteoporose. As investigações iniciais em todos os doentes com osteoporose devem incluir hemograma completo, testes de função renal e hepática, proteinograma, doseamentos séricos de cálcio, fósforo, PTHi, 25-OH-Vitamina D, TSH, testosterona total e cálcio urinário. Outros testes devem ser solicitados com base na história clínica e no exame físico e ainda se indicados por alterações nos exames iniciais.[10] A avaliação analítica confirmou a suspeita diagnóstica inicial, demonstrando níveis de testosterona plasmática baixos e gonadotrofinas aumentadas, compatível com hipogonadismo hipergonadotrófico; caracteriza-se por disfunção testicular que impede a produção de testosterona em níveis fisiológicos em adultos do sexo masculino. Está associado a níveis séricos de testosterona baixos, espermatogénese deficiente e níveis aumentados de gonadotrofinas. As principais causas incluem: síndrome de Klinefelter, criptorquidia unilateral ou bilateral, orquite, irradiação testicular, quimioterapia, fármacos como corticosteroides e quetoconazol, torção e traumatismos testiculares.[11]

O estudo do cariótipo do sangue periférico do doente identificou uma aneuploidia dos cromossomas sexuais em todas as células analisadas, especificamente um cromossoma X e um cromossoma Y supranumerários, correspondendo à síndrome 48,XXYY. Assim, esta alteração cromossómica, foi identificada como a causa do hipogonadismo.

As anomalias cromossómicas são frequentes em humanos, sendo as aneuploidias o tipo de anomalia cromossómica mais comum e com maior importância clínica por serem consideradas a principal causa genética de atraso global do desenvolvimento/perturbação do desenvolvimento intelectual.[12] As aneuplodias são alterações no número de cromossomas que se caracterizam pela perda ou ganho de um ou mais cromossomas.[13] As aneuplodias dos cromossomas sexuais, são um grupo de doenças em que existe pelo menos um cromossoma sexual extra ou ausente[14]; ocorrem em 1 em 400 nados-vivos, sendo a síndrome de Klinefelter (47,XXY) a que ocorrre com maior frequência e, portanto, uma das mais estudadas.[15] Outras aneuplodias com a presença de dois ou mais cromossomas sexuais extras são raras e menos conhecidas. É o caso das síndromes 48,XXYY, 48,XXXY e 49,XXXXY.[16] Estas síndromes eram inicialmente consideradas variantes da síndrome de Klinefelter por partilharem características semelhantes, como estatura alta e hipogonadismo hipergonadotrófico. Porém, atualmente são consideradas entidades diferentes pois estão associadas a características adicionais como risco mais elevado de malformações congénitas e de perturbações e sintomas neuropsiquiátricos e do neurodesenvolvimento.[1,17]

A síndrome 48,XXYY consiste na presença de dois cromossomas sexuais extras, um X e um Y.[1] É considerada rara, com uma prevalência de cerca de 1 em cada 18 000 a 50 000 nados-vivos do sexo masculino.[18] A presença de um cromossoma X extra origina disgenesia testicular, hipogonadismo hipergonadotrófico, risco aumentado de malformações congénitas e envolvimento neuropsicológico.[19] Algumas das características associadas a esta síndrome são: alta estatura, membros inferiores longos, clinodactilia do quinto dedo, leitos ungueais curtos, pés planos, hiperextensibilidade articular, cotovelos proeminentes com cúbito varo e dismorfias faciais como hipertelorismo, pregas epicânticas, fendas palpebrais inclinadas para cima e pálpebras encapuzadas. Também são frequentes as patologias do foro dentário como cáries, esmalte fino, má oclusão e taurodontismo, com necessidade de múltiplos procedimentos odontológicos e de ortodontia. Os doentes apresentam ainda níveis plasmáticos elevados de FSH e LH e baixos de testosterona. A ocorrência de tremor, alergias e asma também foram descritas, bem como perturbação do espectro do autismo e perturbação de défice de atenção hiperactividade (PDAH). Indivíduos com a síndrome 48,XXYY podem ter também perturbações da fala e da linguagem, dificuldades socioemocionais, atraso global do desenvolvimento/perturbação do desenvolvimento intelectual e diminuição das capacidades visuais e perceptivas; além disso, são mais propensos a ter sintomas de hiperatividade e impulsividade. Ao contrário da síndrome de Klinefelter, que é difícil de diagnosticar antes da puberdade, a síndrome 48,XXYY é frequentemente diagnosticada mais cedo (em média aos 7 anos de idade) devido ao atraso no desenvolvimento psicomotor que é observado principalmente entre o 2º e o 5º anos de vida.[20]

Um estudo com o objetivo de descrever as experiências diagnósticas vividas pelos pais de 76 crianças com a síndrome 48,XXYY, mostrou que a média da idade do diagnóstico foi 7,6 anos e que em 93% dos doentes o atraso no desenvolvimento foi a primeira característica que chamou a atenção dos pais.[21]

No caso apresentado, a avaliação diagnóstica teve início apenas aos 46 anos de idade, durante a investigação na Consulta Multidisciplinar de Osteoporose Fraturaria, levando a um diagnóstico muito mais tardio do que o descrito na literatura e por um motivo diferente daquele que habitualmente leva ao diagnóstico destes casos, as fraturas osteoporóticas. O tratamento do doente envolveu medicação anti-osteoporótica com o intuito de melhorar a massa óssea e evitar novas fraturas, bem como o controlo da causa secundária, ou seja, do hipogonadismo, com o objectivo de elevar os níveis de testosterona. Sabe-se que o tratamento com testosterona reduz moderadamente a reabsorção óssea e induz um aumento modesto da densidade mineral óssea da coluna lombar e do fémur proximal. Neste doente, com duas fracturas osteoporóticas major e risco fracturário elevado o tratamento anti-osteoporótico era mandatório. Sendo os bisfosfonatos os fármacos de primeira linha no tratamento da osteoporose masculina, a escolha do ácido zoledrónico baseou-se por um lado na presença de esofagite de refluxo e por outro na necessidade de assegurar a eficácia terapêutica com a via parentérica num doente com perturbação do desenvolvimento intelectual e institucionalizado. A terapia de reposição com testosterona é a principal opção de tratamento para o hipogonadismo hipergonadotrófico. A restauração dos níveis normais de testosterona pode melhorar a massa muscular, aumentar a densidade mineral óssea, manter a acuidade mental e restaurar

a líbido, principalmente em homens idosos.[22-24] Um ano após o início do tratamento, o CTX, o P1NP e a osteocalcina reduziram respectivamente para 0,17, 28,6 e 11,1 ng/mL.

Concluindo, a síndrome 48,XXYY, é uma entidade clínica e genética distinta da síndrome de Klinefelter devido à sua associação a diversas patologias médicas e a maior complexidade do seu envolvimento psicológico e neurológico, com um quociente de inteligência médio mais baixo. Embora os seus sinais e sintomas sejam mais marcantes, o diagnóstico ainda é, em alguns casos, provavelmente tardio, já em idade adulta. Neste doente, o diagnóstico precoce poderia ter corrigido o hipogonadismo e evitado a ocorrência das fracturas osteoporóticas.

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References / Referências

1. Tartaglia N, Davis S, Hench A, Nimishakavi S, Beauregard R, Reynolds A, et al. A new look at XXYY syndrome: medical and psychological features. Am J Med Genet A. 2008;146A:1509-22. doi: 10.1002/ajmg.a.32366.
2. Demirhan O. Clinical findings and phenotype in a toddler with 48,XXYY syndrome. Am J Med Genet A. 2003;119A:393-4. doi: 10.1002/ajmg.a.20015.
3. Emkey GR, Epstein S. Secondary osteoporosis: pathophysiology & diagnosis. Best Pract Res Clin Endocrinol Metab. 2014;28:911-35. doi: 10.1016/j.beem.2014.07.002.
4. Sweet MG, Sweet JM, Jeremiah MP, Galazka SS. Diagnosis and treatment of osteoporosis. Am Fam Physician. 2009;79:193-200.
5. Banu J. Causes, consequences, and treatment of osteoporosis in men. Drug Des Devel Ther. 2013;7:849-60. doi: 10.2147/DDDT.S46101.
6. Banu J. Causes, consequences, and treatment of osteoporosis in men. Drug Des Devel Ther. 2013;7:849-60. doi: 10.2147/DDDT.S46101.
7. Hofbauer LC, Hamann C, Ebeling PR. Approach to the patient with secondary osteoporosis. Eur J Endocrinol. 2010;162:1009-20. doi: 10.1530/EJE-10-0015.
8. Fitzpatrick LA. Secondary causes of osteoporosis. Mayo Clin Proc. 2002;77:453-68. doi: 10.4065/77.5.453.
9. Yazbek M, Neto J. Osteoporose e outras doenças metabólicas no idoso. Einstein. 2008;S74-S78.
10. Premaor MO, Compston JE. Testing for secondary causes of osteoporosis. BMJ. 2010;341:c6959. doi: 10.1136/bmj.c6959.
11. Richard-Eaglin A. Male and Female Hypogonadism. Nurs Clin North Am. 2018;53:395-405. doi: 10.1016/j.cnur.2018.04.006.
12. Hassold T, Abruzzo M, Adkins K, Griffin D, Merrill M, Millie E, et al. Human aneuploidy: incidence, origin, and etiology. Environ Mol Mutagen. 1996;28:167-75. doi: 10.1002/(SICI)1098-2280(1996)28:3<167::AID-EM2>3.0.CO;2-B.
13. Huettel B, Kreil DP, Matzke M, Matzke AJ. Effects of aneuploidy on genome structure, expression, and interphase organization in Arabidopsis thaliana. PLoS Genet. 2008;4:e1000226. doi: 10.1371/journal.pgen.1000226.
14. Visootsak J, Rosner B, Dykens E, Tartaglia N, Graham JM Jr. Behavioral phenotype of sex chromosome aneuploidies: 48,XXYY, 48,XXXY, and 49,XXXXY. Am J Med Genet A. 2007;143A:1198-203. doi: 10.1002/ajmg.a.31746.
15. Abedi M, Salmaninejad A, Sakhinia E. Rare 48, XYYY syndrome: case report and review of the literature. Clin Case Rep. 2017;6:179-84. doi: 10.1002/ccr3.1311.
16. Visootsak J, Graham JM Jr. Klinefelter syndrome and other sex chromosomal aneuploidies. Orphanet J Rare Dis. 2006;1:42. doi: 10.1186/1750-1172-1-42.
17. Atik T, Çoğulu Ö, Özkınay F. A rare sex chromosome aneuploidy: 48,XXYY syndrome. Turk Pediatri Ars. 2016;51:106-9. doi: 10.5152/TurkPediatriArs.2016.1551.
18. Fernández-Pombo A, Millán-Tejedor PS, Guillín-Amarelle C, Castro AI, Guinarte-Cabada JC, Ventura-Victoria M, et al. Morbid Obesity and Psychiatric Disorders Hiding a Sex Aneuploidy: A Case of Late Diagnosis of 48,XXYY Syndrome," 2017. [Online]. [accessed Jan 2021] Available: https://scitechnol.com/peer-review/morbid-obesity-and-psychiatric-disorders-hiding-a-sex-aneuploidy-a-case-of-late-diagnosis-of-48xxyy-syndrome-wwho.pdf.
19. Li J, Zhen L, Pan M, Li DZ. First prenatal case of 48,XXYY syndrome detected by maternal cell-free DNA testing. J Obstet Gynaecol. 2020;40:270-2. doi: 10.1080/01443615.2019.1607268.
20. Chandra S, Galanter CA, Weiss KJ. Problematic Sexual Behavior in a Patient of 48, XXYY Syndrome: A Case Report. J Child Dev Disord. 2016; 2:2. doi: 10.4172/2472-1786.100018.
21. Visootsak J, Ayari N, Howell S, Lazarus J, Tartaglia N. Timing of diagnosis of 47,XXY and 48,XXYY: a survey of parent experiences. Am J Med Genet A. 2013;161A:268-72. doi: 10.1002/ajmg.a.35709.
22. Kumar P, Kumar N, Thakur DS, Patidar A. Male hypogonadism: Symptoms and treatment. J Adv Pharm Technol Res. 2010;1:297-301. doi: 10.4103/0110-5558.72420.
23. Pinsky MR, Hellstrom WJ. Hypogonadism, ADAM, and hormone replacement. Ther Adv Urol. 2010;2:99-104. doi: 10.1177/1756287210369805.
24. Rao SS, Budhwar N, Ashfaque A. Osteoporosis in men. Am Fam Physician. 2010;82:503-8.

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Imagens em Endocrinologia

Yellow Skin as a Rare Diabetes Mellitus's Manifestation

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Pele Amarela como Manifestação Rara da Diabetes Mellitus

Palavras-chave:
Alterações da Pigmentação/etiologia;
Complicações da Diabetes;
Dermatoses da Mão/etiologia;
Dermatoses do Pé/etiologia;
Diabetes Mellitus Tipo 2/complicações.

Hospitalized 76-year-old female with long-time known type 2 (non-insulin-dependent) diabetes mellitus, with organ damage (retinopathy). During internment for confusional syndrome with 1 month of duration, evolves with hyperglycemia of difficult control and yellow palms and soles (Image 1- left foot plant; Image 2 - white arrow, left palm compared with normal palm on the left of image). No jaundice or other skin alterations associated were found. From the complementary exams performed, glycated hemoglobin of 7.4%, with serum bilirubin, renal and thyroid functions within normal limits. Additionally, normal serum vitamin A (0.4 ug/mL) and elevated carotenes (5973 ug/L), with no history of excessive consumption of carotenes-rich foods.

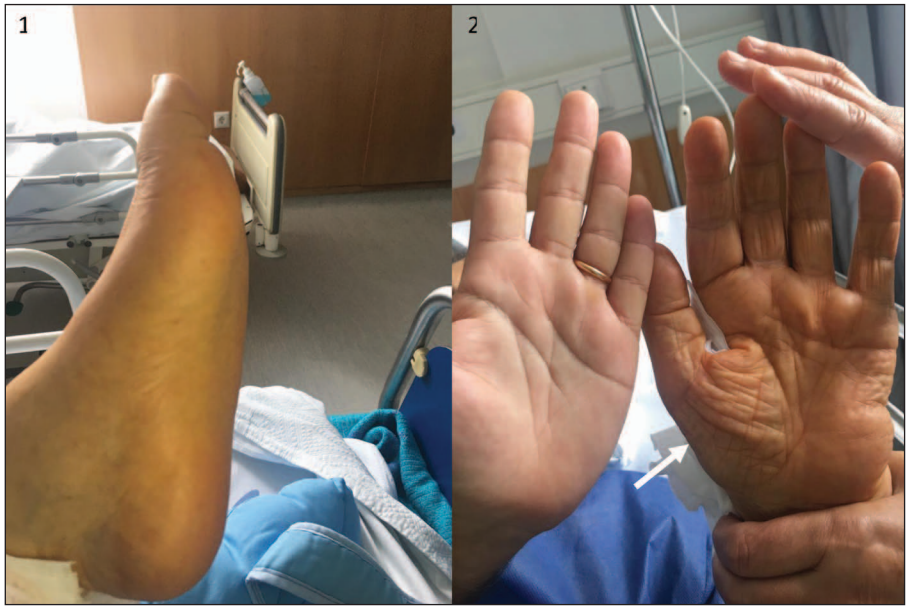

Figure 1. Yellow palms and soles (1- right foot; 2 - arrow, left palm compared with normal palm on the right).

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Yellow skin can occur in association with carotenemia, hypothyroidism, diabetes mellitus, and liver or kidney disease.[1] Many individuals with diabetes have elevated serum carotene levels, but only 10% of these individuals exhibit yellowing of the skin.[2]

This alteration is speculated that the conversion of carotenes to vitamin A in the liver and duodenum is deficient in diabetes. The resultant excess carotene being more lipid soluble gets accumulated in stratum corneum (outermost layer of the epidermis) owing to its high lipid content, imparting yellowish color to the skin.[3]

The patient was treated with insulin and oral hypoglycemic agents with an improvement in the glycemic measures and yellow skin discoloration during hospitalization.

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AC: revisão crítica e aprovação final.

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References / Referências

1. Lin JN. Images in clinical medicine. Yellow palms and soles in diabetes mellitus. N Engl J Med. 2006;355:1486. doi: 10.1056/NEJMicm050780.
2. Julka S, Jamdagni N, Verma S, Goyal R. Yellow palms and soles: A rare skin manifestation in diabetes mellitus. Indian J Endocr Metab. 2013;17:S299-300. doi: 10.4103/2230-8210.119625.
3. Guliani A, Kumar S, Bishnoi A. Yellow palms with underlying type II diabetes mellitus. Indian Dermatol Online J. 2021;12:484-5. doi: 10.4103/idoj.IDOJ_129_20.

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Imagens em Endocrinologia

Angioedema Secondary to Exenatide

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Exenatide/adverse effects.

Angioedema Associado ao Exenatide

Palavras-chave:
Angioedema/induzido quimicamente;
Diabetes Mellitus Tipo 2/tratamento farmacológico;
Exenatide/efeitos adversos.

Exenatide extended release is a weekly subcutaneous injectable glucagon-like peptide-1 (GLP-1) receptor agonist approved by European Medicines Agency (EMA) in 2011.[1] The mechanism of action involves the enhancement of insulin secretion from pancreatic beta-cells, the delaying of gastric emptying and the suppression of glucagon secretion which is known to be inappropriately elevated in patients with type 2 diabetes, leading to lower glucagon concentrations and therefore to decreased hepatic glucose output. The most frequently reported adverse reactions were nausea, diarrhea and injection site reactions (such as pruritus, nodules, erythema). Interestingly, angioedema is documented as a potential side effect of exenatide by its manufacturer however its frequency of occurrence remains unknown[1] and only one case has been reported in literature.[2] Angioedema is a self-limited subcutaneous or submucosal swelling caused by a localized increase in microvascular permeability. Angioedema subdivides in three main categories: histamine-, leukotriene-, and bradykinin-mediated. Allergic angioedema (or histamine-mediated) is one of the most common causes of angioedema and can be triggered by exposure to certain foods, drugs or insect bites.[3]

A 43-year-old woman with a history of diabetes mellitus admitted to the emergency room with an exuberant progressive swelling of the lips and periorbital region, associated with pruritic rash on the chest and abdomen with a reported 3 days of evolution. She had no history of allergies, trauma or family history of angioedema. No other alterations on examination were found. The patient initiated an extended release exenatide 13 days before admission and had her second dose 6 days prior. The diagnosis of angioedema secondary to exenatide was assumed and she was treated with antihistamines and corticosteroids, with resolution of symptoms. The patient was discharged the following day with a course of corticosteroids and antihistamines, given the prolonged half-life of exenatide, and an indication to discontinue exenatide. She made a full recovery.

Regarding our patient's symptoms (angioedema associated with pruritic rash), the temporal sequence (2 weeks post-first injection, which concurs with the first peak plasma concentration of exenatide),[4] the resolution with conventional treatment (antihistamines and steroids) and the negative family history, allergic angioedema secondary to exenatide was assumed. The underlying mechanism for the development of drug-associated angioedema is multifactorial[5] and since GLP-1 agonists induced angioedema is a rarely reported adverse effect, this mechanism remains uncertain.

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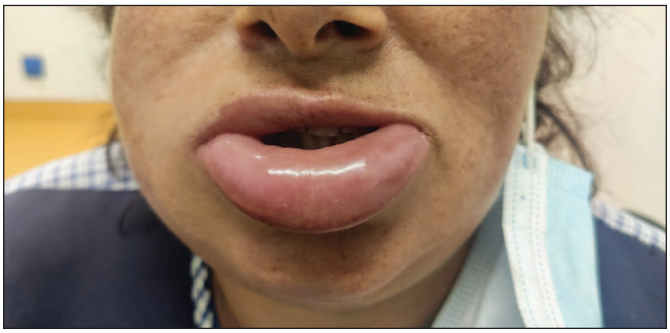

Figure 1. Angioedema – Front view: Exuberant swelling of the lower lip, right-side of upper lip and face.

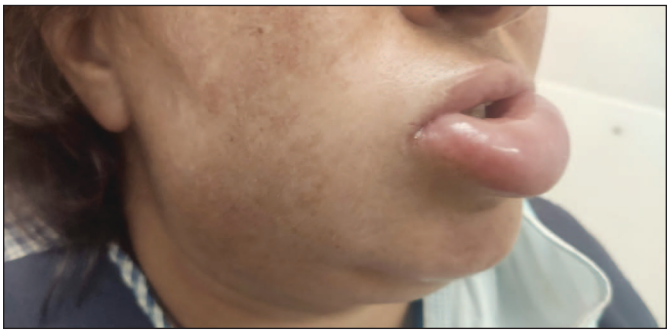

Figure 2. Angioedema – Lateral view: Exuberant swelling of the lower lip, right-side of upper lip and face.

This case aims to raise awareness to the extremely rare potential adverse effect of angioedema secondary to exenatide, which has only been reported once in literature. Moreover, this case reminds us to a fundamental detail, the necessity of prolonging the course of treatment due to the prolonged half-life of exenatide.

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References / Referências

1. European Medicines Agency. European Public Assessment Report for Bydureon (exenatide weekly). EMEA/H/C/002020 - II/0074 . [accessed in October 2022] Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/bydureon.
2. Mahfooz F, Aylor K, Mathew J Jr, Reichmuth M. Extending our understanding of exenatide: a rare case of angio-oedema. BMJ Case Rep. 2021;14:e235663. doi: 10.1136/bcr-2020-235663.
3. Tarbox JA, Bansal A, Peiris AN. Angioedema. JAMA. 2018;319:2054. doi: 10.1001/jama.2018.4860.
4. Bhavsar S, Mudaliar S, Cherrington A. Evolution of exenatide as a diabetes therapeutic. Curr Diabetes Rev. 2013;9:161-93. doi: 10.2174/1573399811309020007.
5. Weldon D. Differential diagnosis of angioedema. Immunol Allergy Clin North Am. 2006;26:603-13. doi: 10.1016/j.iac.2006.09.006.

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Thyroid Fine Needle Aspiration Biopsy Complicated with Massive Bilateral Hematoma Under Clopidogrel

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Hematoma;
Thyroid Gland.

A 67-year-old woman with arterial hypertension and nontoxic multinodular goitre underwent ultrasound-guided fine-needle aspiration biopsy (FNAB) using a 25-gauge needle on the two nodules in the left lobe (two punctures on each nodule): an isoechogenic solid nodule with regular margins measuring 37.4x24x25 mm [European Thyroid Imaging and Reporting Data System (EU-TIRADS) 3[1]] and a slightly hypoechogenic solid nodule with regular margins measuring 17.6x15x14 mm (EU-TIRADS 4[1]). She had no previous history of bleeding and was recently being treated with clopidogrel without having reported it to endocrinologist. Thirty minutes later, the patient developed severe neck pain and dysphagia. The patient applied ice at the biopsy site and ultrasound evaluation showed a hematoma anterior to the thyroid, with larger volume on the right side (34.1x19.2x15.4 mm) than on the left (22.1x21.6x6.7 mm) (Fig. 1). The esophageal pathway was intact (Fig. 2). She kept surveillance at emergency department, with successful

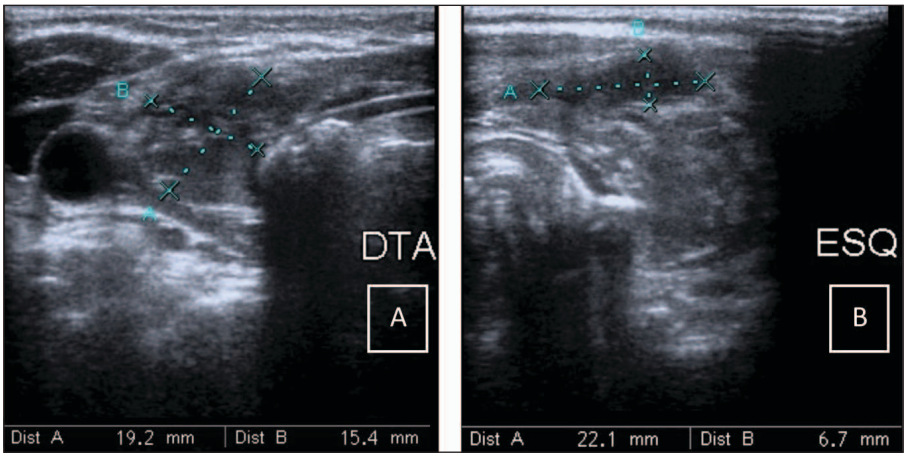

Figure 1. Ultrasound showed a bilateral thyroid hematoma anterior to the thyroid after fine-needle aspiration biopsy in a patient taking clopidogrel. Image A shows the hematoma on the right side and image B shows the hematoma on the left side.

Citologia Aspirativa por Agulha Fina da Tiróide Complicada com Hematoma Bilateral Maciço sob Clopidogrel

Palavras-chave:
Citologia Aspirativa por Agulha Fina;
Tiróide;
Hematoma;
Clopidogrel.

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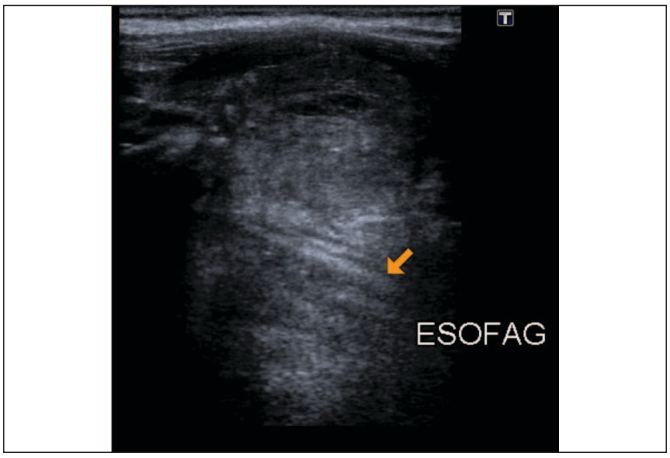

Figure 2. Ultrasound showed the esophageal pathway intact.

resolution of the hematoma. Complete blood count and coagulation tests showed no changes.

Ultrasound-guided thyroid FNAB is a safe procedure and antiplatelet drugs, such as clopidogrel, can be maintained.[2] Hematomas are the most common complications, but can be adequately treated with compression if the physician advices the patient.[3] In this case, we can speculate that clopidogrel is only an extra risk factor and the hematoma occurred as a complication of the FNAB itself. Paradoxically, the largest hematoma volume was found on the side opposite the biopsy site, which could be explained by the effective application of compression and ice at the biopsy site. Reassessment thyroid ultrasound after FNAB is important in patients who develop symptoms such as severe pain or other sudden symptoms to detect serious complications early.

Contributorship Statement / Declaração de Contribuição:

II: conception, data collection, and draft manuscript preparation.
TA: conception and draft manuscript preparation.
All authors reviewed and approved the final version of the manuscript.

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Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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References / Referências

1. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. Eur Thyroid J 2017;6:225-37. doi: 10.1159/000478927.
2. Khadra H, Kholmatov R, Monlezun D, Kandil E. Do anticoagulation medications increase the risk of haematoma in ultrasound-guided fine needle aspiration of thyroid lesions? Cytopathology 2018;29:565-8. doi: 10.1111/cyt.12608.
3. Polyzos SA, Anastasilakis AD. Clinical complications following thyroid fine-needle biopsy: a systematic review. Clin Endocrinol. 2009;71:157-65. doi: 10.1111/j.1365-2265.2009.03522.x.

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Errata / Erratum

Real-World Flash Glucose Monitoring Patterns in Portugal: The Association between Self-Monitoring Frequency and Measures of Glycemic Control

Davide Carvalho, Rui Duarte, Kalvin Kao, Laura Brandner

[Rev Port Endocrinol Diabetes Metab. 2022;17(3-4):26-32] foi publicado com imagem errada.

Na página 29, onde se vê "Figure 3":

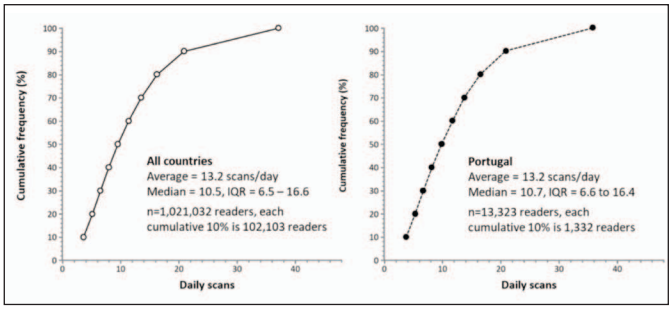

Figure 3. Percent time in range 70-180 mg/dL and above range with glucose >180 mg/dL by sensor scanning frequency.

Data are mean % time in range 70-180 mg/dL and > 180 mg/dL observed for each of the 10 ranked scan-frequency groups of readers, from lowest to highest mean scans/day. Each point on the graph represents 10% of all readers.

All-countries refers to the full analysis set for all countries in the multinational dataset.

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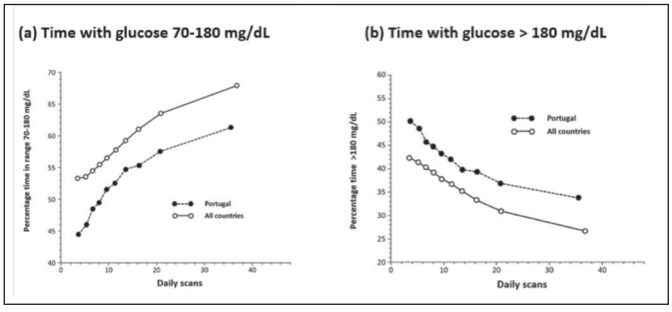

Figure 3. Percent time in range 70-180 mg/dL and above range with glucose >180 mg/dL by sensor scanning frequency.

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Article structure

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient detail to allow the work to be reproduced.

Article type	Abstract	Keywords	Main text structure	Max. words	Tables/figures	References
Original Article	Max. 350 words; structured (Introduction and Objectives, Methods, Results and Conclusion(s)) Portuguese and English	Up to 6 Portuguese and English	Introduction; Methods; Results; Discussion; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 60
Review Article	Max. 350 words; unstructured Portuguese and English	Up to 6 Portuguese and English	Introduction; thematic sections at the discretion of the authors; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 100
Systematic Review	Max. 350 words; structured Portuguese and English	Up to 6 Portuguese and English	PRISMA	4000	Total up to 6	Up to 100
Case Report	Max. 150 words; unstructured Portuguese and English	Up to 6 Portuguese and English	Introduction; Case report; Discussion; Conclusion(s) (optional); References; and figure legends, if any	2000	Total up to 4	Up to 25
Images in Endocrinology	None	Up to 6 Portuguese and English	Unstructured	500	Total up to 4	Up to 5
Editorial	None	None	Unstructured	1500	Total up to 2	Up to 20
Letter to the Editor	None	Up to 6 Portuguese and English	Unstructured	600	Total up to 1	Up to 10
Current Perspectives	None	Up to 6 Portuguese and English	Unstructured	1200	Total up to 2	Up to 10

Methods already published should be indicated by a reference: only relevant modifications should be described.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusion

The main conclusion of the study may be presented in a short Conclusion section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Artigos de Revisão

Os artigos de revisão são artigos abrangentes que sintetizam ideias antigas e sugerem novas. Abrangem áreas amplas. Podem ser de ciência clínica, investigação ou básica. Embora geralmente por convite do Editor-Chefe, ocasionalmente aceitamos artigos de revisão não solicitados sobre assuntos importantes ou sobre avanços recentes. Antes de submeter uma revisão, pedimos que envie ao Editor-Chefe um breve esboço (não mais de 500 palavras) indicando a importância e novidade do assunto, e por que está qualificado para escrevê-lo. Um convite para submissão não garante aceitação.

Os artigos de revisão não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 100 referências. Um resumo não estruturado com o máximo de 350 palavras.

Revisões Sistemáticas e Meta-Análises

As revisões sistemáticas podem ou não utilizar métodos estatísticos (meta-análises) para analisar e resumir os resultados dos estudos incluídos.

As Revisões Sistemáticas podem ser apresentadas no formato Introdução, Métodos, Resultados, Discussão. O assunto deve ser claramente definido. O objectivo de uma revisão sistemática deve ser produzir uma conclusão baseada em evidências. Nos Métodos devem fornecer uma indicação clara da estratégia de pesquisa da literatura, extracção de dados, classificação das evidências e análise. Deve ser seguida a normativa PRISMA (http://www.prisma-statement.org/).

O texto não deverá exceder 4000 palavras, excluindo um resumo estruturado (máximo de 350 palavras). Não poderá incluir mais de 10 referências, e até 6 tabelas ou figuras**.**

Caso Clínico

O relato de Casos Clínicos deve incluir as seguintes seções: Introdução, Caso Clínico e Discussão.

O texto não poderá exceder 2000 palavras, e não poderá exceder as 25 referências bibliográficas. Deve incluir um resumo não estruturado, que não exceda 150 palavras.

Deve ser seguida a normativa CARE (http://www.care-statement.org/).

Editoriais

Os Editoriais são da responsabilidade do grupo editorial ou solicitados por convite do Editor-Chefe e constituirão comentários sobre tópicos actuais ou comentários sobre artigos publicados na revista. Não devem exceder as 1200 palavras, um máximo de 20 referências bibliográficas e podem conter uma tabela e uma figura. Não têm resumo.

Cartas ao Editor

As cartas ao Editor consistem em comentários críticos sobre um artigo publicado na revista ou uma nota curta sobre um determinado tópico ou caso clínico. Cartas ao Editor não devem exceder 600 palavras e 10 referências e pode conter uma figura ou tabela. Não têm resumo.

Imagens em Endocrinologia

Esta secção destina-se à publicação de imagens clínicas, radiológicas, histológicas e cirúrgicas relacionadas com casos de endocrinologia, diabetes ou metabolismo.

O título não deve ter mais de oito palavras. Os autores devem ser no máximo quatro. As imagens devem ser de alta qualidade e valor educativo. São permitidas até 4 figuras**.** As legendas devem ser breves e informativas. Setas ou outros símbolos devem ser incluídos conforme necessário para facilitar a compreensão das imagens. O texto não deve exceder 500 palavras, até cinco referências, e deve incluir uma breve história clínica e dados relevantes do exame físico, testes laboratoriais e progressão clínica, conforme apropriado. Não têm resumo.

Perspectiva

Este é o tipo de manuscrito é submetido a convite do Conselho Editorial. Pode abranger uma ampla diversidade de temas relacionados com endocrinologia, diabetes, metabolismo e saúde: problemas atuais ou emergentes, políticas de gestão e saúde, história da medicina, questões de sociedade e epidemiologia, entre outros. Um Autor que deseje propor um manuscrito nesta seção deverá enviar um resumo ao Editor-Chefe, incluindo o título e a lista de autores para avaliação. O texto não deve exceder 1200 palavras, até 10 referências, e até 2 tabelas ou 2 figuras. Não têm resumo.

Guidelines

Os guias de prática clínica não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 100 referências. Resumo até 350 palavras.

Referências

I.Citação no texto

Certifique-se de que todas as referências citadas no texto também estão presentes na lista de referências (e vice-versa). As referências devem ser listadas usando algarismos árabes pela ordem em que são citados no texto.

As referências a comunicações pessoais e dados não publicados devem ser feitas diretamente no texto e não devem ser numeradas. Citação de uma referência como "in press" implica que o item tenha sido aceite para publicação. Os nomes das revistas devem ser abreviados de acordo com o estilo da Medline.

As referências a artigos publicados em revistas devem incluir o nome do primeiro autor seguido dos nomes dos restantes autores, o título do artigo, o nome da revista e o ano de publicação, volume e páginas.

Certifique-se de que os dados fornecidos nas referências estão corretos. Ao copiar referências, tenha cuidado porque já podem conter erros.

A lista de referências deve ser adicionada como parte do texto, nunca como uma nota de rodapé. Códigos específicos do programa de gestão de referências não são permitidos.

II. Formato

Uma descrição detalhada dos formatos de diferentes tipos de referência pode ser consultada em ICMJE *Recommendations* (http://www.icmje.org/recommendations/). Liste todos os autores se houver seis ou menos. *Et al* deve ser adicionado se houver mais de seis autores. Título do artigo, nome da revista, ano, volume e páginas.

III. Estilo de referência

Texto: Indicar as referências no texto por número (s) em expoente. Os autores podem ser referidos, mas o número de referência deve ser sempre dado.
Lista: Ordene as referências na lista pela ordem em que aparecem no texto
Exemplos:
Referência de artigo:

1. Isidori AM, Sbardella E, Zatelli MC, Boschetti M, Vitale G, Colao A, et al. Conventional and nuclear medicine imaging in ectopic Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2015;100:3231-44.

Referência de livro:

2.Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 Health Survey: standard & acute forms. Lincoln: Quality Metric Incorporated; 2000.

Referência de capítulo de livro:

3. Castellano Barca G, Hidalgo Vicario M, Ortega Molina M. Transtorno del comportamento alimentário. In: Castellano Barca G, Hidalgo Vicario M, Redondo Romero A, editores. Medicina de la adolescência – atención integral. 2ª ed. Madrid: Ergon; 2004. p.415-29.

Referências Web:

4. No mínimo, o URL completo deve ser dado e a data em que o documento foi consultado. Qualquer outra informação, se conhecida (nomes de autor, datas, referência a uma publicação de origem, etc.), também deve ser dada.

Notas de Rodapé

As notas de rodapé devem ser evitadas. Quando imprescindíveis, devem ser numerados consecutivamente e aparecer ao pé da página apropriada.

Agradecimentos (facultativo)

Devem vir após o texto, e antes das referências, tendo como objectivo agradecer a todos os que contribuíram para o estudo mas que não têm peso de autoria. Nesta secção é possível agradecer a todas as fontes de apoio, quer financeiro, quer tecnológico ou de consultadoria, assim como contribuições individuais.

Abreviaturas

Não use abreviaturas ou acrónimos no título e no resumo e limite o seu uso. Abreviaturas não consagradas devem ser definidas na primeira utilização, por extenso, logo seguido pela abreviatura entre parenteses. A menos que a sigla seja uma unidade padrão de medição. Uso excessivo e desnecessário de acrónimos e abreviaturas deve ser evitado.

Unidades de Medida

Devem ser utilizadas as unidades Sistema Internacional de Unidades. As medidas de comprimento, altura, peso e volume devem ser expressas em unidades do sistema métrico (metro, quilograma ou litro) ou seus múltiplos decimais. As temperaturas devem ser dadas em graus Celsius (ºC) e a pressão arterial em milímetros de mercúrio (mm Hg) ou a hemoglobina em g/dL. Todas as medições hematológicas ou bioquímicas serão referidas no sistema métrico de acordo com o Sistema Internacional de Unidades (SI).

Nomes de Medicamentos

Identifique com precisão todos os medicamentos e produtos pelo nome genérico. Não é recomendável a utilização de nomes comerciais de fármacos (marca registrada), mas quando a utilização for imperativa, o nome do produto deverá vir após o nome genérico, entre parênteses, em minúscula, seguido do símbolo que caracteriza marca registada, em sobrescrito (®).

Tabelas e Figuras

Tabelas/Figuras devem ser numerados na ordem em que são citadas no texto e assinaladas em numeração árabe e com identificação, Figura/Tabela.

Cada figura e tabela incluídas no trabalho têm de ser referidas no texto: Uma resposta imunitária anormal pode estar na origem dos sintomas da doença (Fig. 2). Esta associa-se a outras duas lesões (Tabela 1).

Figura: Quando referida no texto é abreviada para Fig., enquanto Tabela não é abreviada. Nas legendas ambas as palavras são escritas por extenso.

Cada tabela e figura deve ser acompanhada da respectiva legenda, sucinta e clara. As legendas devem ser auto-explicativas (sem necessidade de recorrer ao texto).

Em relação aos gráficos deve ser explícito se a informação inclui valores individuais, médias ou medianas, se há representação do desvio padrão e intervalos de confiança e o tamanho da amostra (n).

As fotografias deverão incluir identificadores (setas e asteriscos). Poderão ser publicadas fotografias a cores, desde que consideradas essenciais.

Cada tabela deve ser utilizada para mostrar resultados, apresentando listas de dados individuais ou sumariando os mesmos, não devendo no entanto constituir duplicação dos resultados descritos no texto. Devem ser acompanhadas de um título curto mas claro e elucidativo. As unidades de medida usadas devem ser indicadas (em parêntesis abaixo do nome que encabeça cada categoria de valores) e os números expressos devem ser reduzidos às casas decimais com significado clínico.

Para as notas explicativas nas tabelas devem ser utilizados os seguintes símbolos e sequência: *, †, ‡, §, ||, ¶, **, ††, ‡‡ .

Se fotografias de doentes forem usadas, estes não devem ser identificáveis ou as fotografias devem ser acompanhadas de autorização por escrito para usá-las.

As imagens a cores são reproduzidas gratuitamente.

Princípios gerais:

• Numere as ilustrações de acordo com a sua sequência no texto.

• Forneça as legendas das ilustrações separadamente.

• Dimensione as ilustrações próximas das dimensões desejadas da versão publicada.

• Envie cada ilustração em ficheiro separado.

A inclusão de figuras e/ou tabelas já publicadas, implica a autorização do detentor de *copyright* (autor ou editor).

A submissão deve ser feita separadamente do texto, conforme as instruções da plataforma.

Os ficheiros das figuras devem ser fornecidos em alta resolução, 800 dpi mínimo para gráficos e 300 dpi mínimo para fotografias.

A publicação de ilustrações a cores é gratuita.

Material gráfico deve ser entregue em um dos seguintes formatos:
JPEG (. Jpg)
Portable Document Format (. Pdf)
PowerPoint (.ppt)
TIFF (. Tif)
Excel

Permissão para publicação: No caso de publicação de tabelas de livros ou revistas os autores são responsáveis por obter permissão, junto dos autores dos trabalhos de onde forem reproduzidos, para a referida publicação, e terão de a apresentar na submissão.

Ficheiros Multimedia

Os ficheiros multimedia devem ser enviados em ficheiro separado com o manuscrito. O material multimedia deve seguir os padrões de qualidade de produção para publicação sem a necessidade de qualquer modificação ou edição. Os ficheiros aceitáveis são: formatos MPEG, AVI ou QuickTime.

Anexos/ Apêndices

Quando necessário, os anexos devem ser utilizados para apresentar inquéritos longos ou detalhados, descrições de extensos cálculos matemáticos e / ou listas de itens. Devem ser colocados depois da lista de referências, se necessário, com legendas. Anexos longos, tais como algoritmos, pesquisas e protocolos, serão publicados apenas *online*; o URL será fornecido no artigo impresso onde o anexo é citado.

Se houver mais de um apêndice, eles devem ser identificados como A, B, etc. As fórmulas e equações em apêndices devem ser numeradas separadamente: Eq. (A.1), Eq. (A.2), etc.; Em apêndice posterior, a Eq. (B.1) e assim por diante. Da mesma forma para tabelas e figuras: Tabela A.1; FIG. A.1, etc.

Estilo

Rev Port Endocrinol Diabetes Metab segue AMA Manual Style (10ª edição).

Última revisão **Janeiro 2022**